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SPONTANEOUS PERIODIC HYPOTHERMIA[1]

By R. S. DUFF, P. C. FARRANT, V. M. LEVEAUX, and S. M. WRAY

(From the Department of Medicine, the University of Sheffield, and the Derbyshire Royal Infirmary)

In man spontaneous hypothermia is exceedingly uncommon in the adult. Considerable falls in temperature may occur in diseases that profoundly interfere with metabolism, such as myxoedema, and as a result of certain focal lesions of the hypothalamus and adjacent areas of the brain. In lesions of the latter description the hypothermia is usually a terminal event, of comparatively short duration, sometimes following surgical intervention. In two instances a meningioma (Ratner, 1925) and a craniopharyngioma (Obregia, Dimolescu, and Constaninescu, 1932), both adjacent to the third ventricle, were found at autopsy. Davison and Selby (1935) described a patient who had polydipsia and polyuria for 13 years before developing hypothermia terminally; an angioma was found arising from the floor of the third ventricle. Kaplan, Hart, and Browder (1952) described a patient with a glioma of the mid-brain who developed hypothermia after craniotomy, but autopsy revealed areas of recent softening which included the hypothalamus. Wechsler (1956) quoted an example of hypothermia due to a middle-fossa tumour that impinged on the diencephalon. A malignant vascular tumour caused a low body temperature (and also a raised serum-magnesium level) in an infant girl reported by Sunderman and Haymaker (1947). Three examples of diencephalic neoplasms producing hypothermia were reviewed by Davison and Demuth (1946), but in only one was the temperature quoted. This patient had a hypothalamic angioma; the temperature varied between 90° and 97° F. In a review of the clinical features of 60 cases of hypothalamic disease proved at autopsy, Bauer (1954) found that oral, axillary, or rectal temperatures below 90° F had been recorded in seven patients at some time before death. Dissociation of pulse and temperature was found in three others, and poikilothermia in one. The hypothalamic lesions were mostly neoplastic (craniopharyngioma and astrocytoma predominating), the remainder being inflammatory or degenerative.

Of a different character were the two cases reported by Hines and Bannick (1934) and by Hoffman and Pobirs (1942). They were men who had episodes of hypothermia recurring annually over periods of 10 and seven years respectively. During these episodes daily falls in temperature to between 91° and 94° F occurred every morning for several weeks. The hypothermia was associated with profound and often disabling sweating lasting for one to two hours;

[1] Received January 11, 1961.

shivering fits followed, and thereafter there was a rapid recovery of normal body temperature. In neither instance was any cause found despite intensive investigation, and the attacks ceased in both patients with the administration of barbiturates. They were otherwise healthy men, who in every respect were normal between the hypothermic attacks. Two further patients with periodic intermittent hypothermia of a similar character are here described.

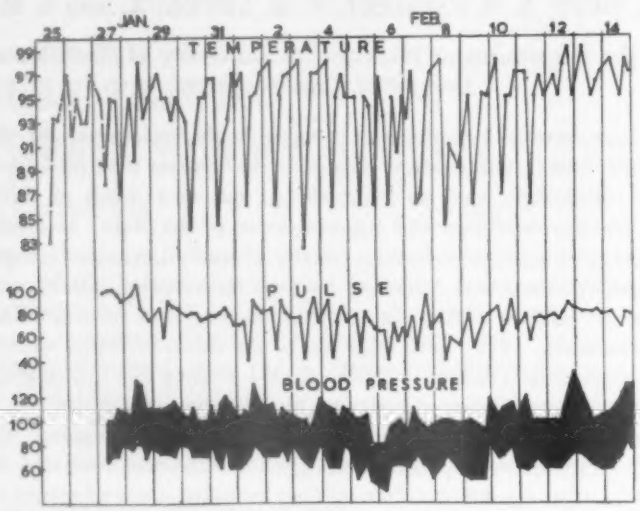

FIG. 1. Case 1. Temperature (°F), pulse-rate, and blood-pressure during three weeks in hospital. The initial interrupted lines indicate rectal, the later (continuous lines) oral temperature.

Case 1. In January 1960 a surface colliery worker aged 30 was admitted to Sheffield Royal Hospital. He complained of periodic attacks of sweating since the age of 10 years. During his Army service in 1949 these sweating attacks were investigated, and a provisional diagnosis of Simmonds's disease was made, although the 17-ketosteroid excretion was reported to be normal. Later admissions to hospital with the same complaint resulted in various diagnoses, including hypoglycaemia and psychoneurosis. One severe attack led to an emergency admission with profound collapse and bradycardia, but he was never completely unconscious. There was no significant past history; the mother suffered from diabetes mellitus, and the father was stated to be an epileptic. The patient himself had three healthy children.

On admission, clinical examination was at first entirely negative. Later, when the patient was sweating, he was difficult to interrogate, appearing to have difficulty both in understanding and in answering questions. Examination of the nervous system revealed sluggish pupil responses and deep tendon reflexes, and absent superficial reflexes. Although the oral temperature was recorded on the ward charts as 97° F, the skin felt very cold, and a low-reading thermometer placed in the rectum registered 85° F. Further temperature recordings during the remainder of his stay in hospital are shown in Fig. 1.

The typical pattern of the sweating attacks was quite distinct. Between 5 a.m. and 6 a.m. he would awaken feeling very hot. The rectal temperature

was then between 97° and 98° F. During the next few hours his skin and bedclothes became drenched with perspiration, and the oral and rectal temperatures fell at the rate of three to four degrees an hour, to reach their lowest point (83° F, and on one occasion 82·3° F), almost exactly at 10 a.m. Simultaneously the blood-pressure fell by 20 to 30 mm. Hg, and the pulse-rate decreased to a frequency of about 40 per minute. At this point the regular rhythm of the heart was sometimes replaced by atrial fibrillation. The patient

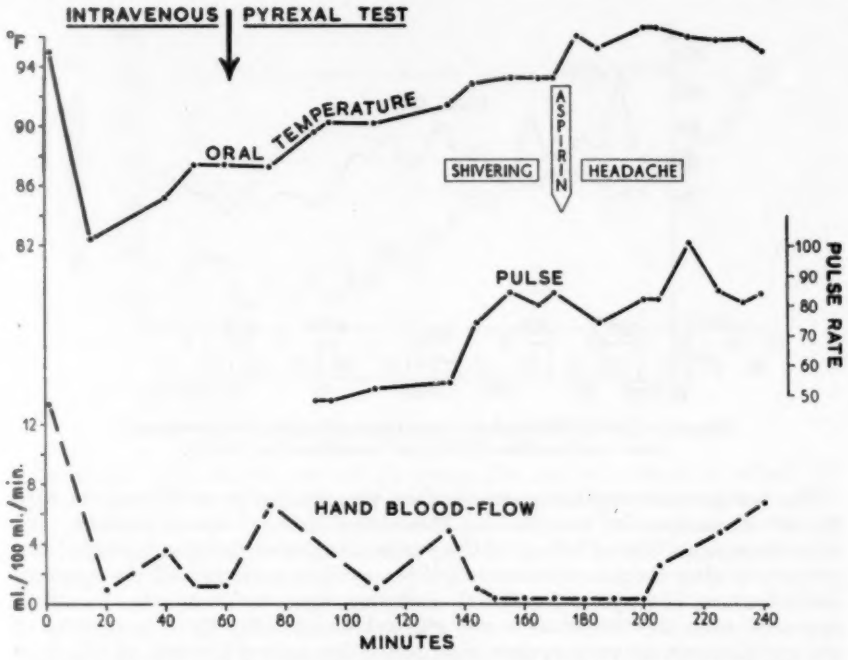

FIG. 2. Case 1. Oral temperature, pulse-rate, and hand blood-flow during the 'pyrexal' test.

remained in this state for about half an hour; the sweating then ceased and he started to shiver, whereupon the temperature, pulse rate, and blood-pressure began to rise, and approached normal levels in the later afternoon. The electrocardiogram taken between attacks was normal, but records during the bouts of sweating showed bradycardia, sometimes atrial fibrillation, prolonged P–R and Q–T intervals, and the presence of 'junctional' waves (Osborn, 1953). The daily fluctuations in temperature continued for 16 days, and then suddenly ceased. They were not related to the ambient temperature or to the prevailing weather, nor were they influenced by the patient's behaviour or activity, or by any emotional stress.

Routine haematological and biochemical investigations, including several estimations of the fasting blood-sugar level, gave normal results. A modified Kepler test, urinary ketosteroid and ketogenic steroid output, corticotrophin stimulation test, and measurements of basal metabolic rate and ^{131}I uptake, all gave results within normal limits. The visual fields, cerebrospinal fluid, and skull X-rays were normal, as was the chest radiograph. The

electroencephalogram was reported as showing theta activity in the anterior leads. A glucose tolerance test during the hypothermic period produced a maximum blood-sugar level of 260 mg. per 100 ml., with slight glycosuria; the blood-sugar then decreased to 30 mg. per 100 ml., and the level was still abnormally low six hours after the start of the test. The test was repeated when the temperature was normal, and an entirely different response was obtained: no conspicuous change in blood-sugar level was recorded after the administration of the glucose.

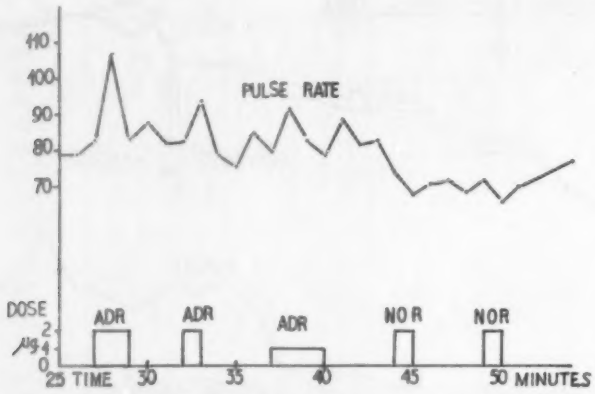

FIG. 3. Case 1. Effect on the heart-rate of minute intravenous doses of adrenaline (ADR) and noradrenaline (NOR).

The temperature-regulating mechanism was studied in collaboration with Dr. K. E. Cooper (of the Medical Research Council Unit at Oxford). An intravenous injection of 0·3 μg. of the purified bacterial pyrogen 'pyrexal' was given, and after the usual latent period the patient exhibited all the symptomatic features of a pyrexial reaction, including rigors and headache, but these appeared while the temperature was still subnormal (Fig. 2). The activity of the sympathetic nervous system was tested by a modification of the heat test of Landis and Gibbon (1933). In this test the blood-flow in the hands is measured plethysmographically before and after the body temperature has been raised by immersing the feet in hot water (113° F, 45° C) for up to one hour. Normally the oral temperature rises above 100° F, and the blood-flow increases more than twofold. When tested in this way the patient exhibited a 15-fold increase in hand circulation, but the oral temperature rose only to 97·7° F, at which point he was sweating so profusely as to be on the point of collapse. This result suggested that the efferent vasomotor pathway was intact, and that the temperature-regulating mechanism was working normally but at a low level.

Cardiac responses to the adrenergic hormones were studied next. During the course of a continuous intravenous saline infusion, amounts of adrenaline and noradrenaline that would not be expected to cause measurable changes in healthy adults (1 to 2 μg.) repeatedly caused transient tachycardia and bradycardia (Fig. 3) respectively. This was thought possibly to indicate hypersensitivity to these substances. The patient has remained well since being discharged from the ward, and no further attacks have yet occurred.

Case 2. A girl of 13 years, previously healthy, was first seen at the Derbyshire Royal Infirmary in 1949, having had several generalized convulsions in

the previous few months. She was the eldest of three children, pregnancy and delivery having been normal, and there was no family history of epilepsy. She was of average intelligence. Physical examination was negative. An electroencephalogram showed bursts of high-voltage slow activity. Skull radiographs were normal, and the blood Wassermann reaction negative. A diagnosis of idiopathic epilepsy was made, and the patient was treated with phenobarbitone and sodium phenytoin. She remained free from fits for the next six years.

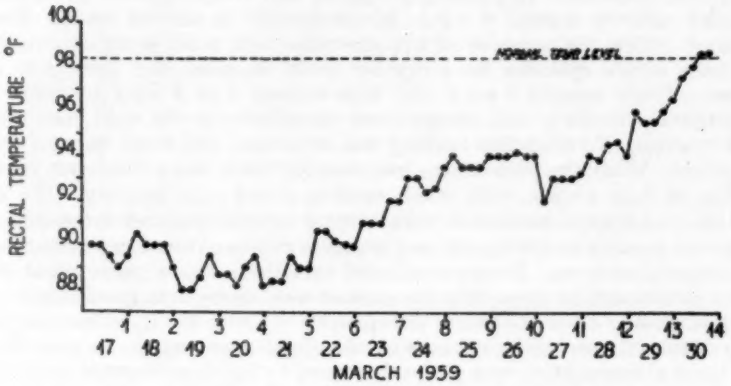

FIG. 4. Case 2. Rectal temperature during one period in hospital.

In March 1957, at the age of 21 years, she had an attack in which she suddenly became unsteady, dazed, and speechless, but not unconscious. The phenytoin had been omitted for a few days. After the attack she remained mentally slow, with slurred speech and unsteadiness of gait. Dexamphetamine sulphate, prescribed by her doctor, had produced no improvement, and two weeks later she was admitted to hospital. For three months previously she had been gaining weight, and more recently her face had become swollen. On examination she was a plump girl, slow of speech and cerebration. The pulse-rate was 40 per minute and regular, and the blood-pressure 100/80. It was found that her rectal temperature was abnormally low, ranging between 87° and 91° F. Clinical examination showed no other abnormality apart from left-sided facial asymmetry. The patient remained in this state, with a low temperature, for five days. Pneumonia then developed, and the rectal temperature gradually rose to normal levels. She made a good recovery from the pneumonia, and the temperature remained normal, at no time having exceeded 99° F. Since then there have been 11 similar attacks requiring admission to hospital, most of them during the winter. On each occasion the clinical state has resembled that seen in March 1957, with mental torpor, bradycardia, hypotension, and a low rectal temperature, often below 93° F. Sometimes facial asymmetry has been noticed. Recovery of normal temperature has occurred at times varying from four days to four weeks after the onset of hypothermia, and has usually been spontaneous. The rectal temperature during one period in hospital is shown in Fig. 4. Numerous investigations have been performed during and between the hypothermic episodes. Routine haematological and biochemical investigations, including an estimation of the fasting blood-sugar level during a period of hypothermia and a serum-cholesterol estimation, gave normal results. A skull radiograph was again normal.

Extensive electroencephalographic studies were made (Dr. W. B. Matthews). The first record was obtained on a four-channel instrument in June 1950, before there had been any evidence of hypothermia. This contained a normal α rhythm at nine cycles per second (c.p.s.), with frequent brief symmetrical paroxysms of generalized high-voltage activity at 3 c.p.s. Between April 1957 and November 1959 16 records were obtained, using an eight-channel instrument. These records were all abnormal. When the patient was fully alert, and with a normal temperature, the records contained symmetrical 9-c.p.s. occipital α rhythm, responsive to opening the eyes, and frequent brief paroxysms of irregular activity around 6 c.p.s., symmetrically in central leads. Records obtained during the episodes of hypothermia were much more abnormal. In the more severe episodes no α rhythm could be seen, and there was much diffuse activity around 6 c.p.s. and high-voltage 2 to 3 c.p.s. activity, most pronounced anteriorly and always more prominent on the right, but without focal features. No sleep fast activity was ever seen, and there were no arousal complexes. When the patient was less retarded there was a dominant posterior rhythm at 7 to 8 c.p.s., with much random 4 to 6 c.p.s. activity. The hypothermia was always associated with mental retardation and drowsiness, and it was not possible to distinguish any separate effects of these two factors on the electroencephalogram. It was concluded that there was a paroxysmal abnormality of subcortical type when the patient was otherwse in good health. This was presumably associated with the epilepsy. During the hypothermic phases gross diffuse abnormalities appeared, with slight asymmetry. It was thought that these abnormalities were probably caused by the hypothermia, and did not provide evidence of a discharging lesion producing the intermittent symptoms.

Estimations of the basal metabolic rate, when the rectal temperature was 93° to 95° F, gave a mean value of −36 per cent. Estimations repeated after the administration of 60 μg. of tri-iodothyronine daily for 10 days gave a value of −18 per cent., but the drug had no effect on the rectal temperature. A standard water-load test showed only 45 per cent. excretion after three hours. The hypertonic saline test (Carter and Robbins, 1947) gave a normal result. Serum electrolytes, and urinary 17-ketosteroid, 17-ketogenic steroid, oestrogen, and gonadotrophin levels, were all within normal limits. Tests of thyroid function with ^{131}I also yielded normal results, the 24-hour uptake being 74 per cent. Electrocardiograms showed bradycardia and prolongation of the P–R and Q–Tc intervals, with variable T-wave inversion over the left ventricle, these findings being usual in hypothermia from other causes (Osborn, 1953).

Injections of adrenaline, noradrenaline, atropine, dexamphetamine sulphate, and chlorpromazine had no effect on the rectal temperature. Immersion in a bath for 30 minutes at a temperature of 110° F produced a rise of rectal temperature of only two degrees, from 95° to 97° F. The rise in temperature after an intravenous injection of a bacterial pyrogen ('pyrifer') was abnormally delayed (Fig. 5). The highest temperature occurred at 37 hours, whereas a normal maximum response would have been expected not more than two hours after the injection. In view of the history of fits and facial asymmetry, lumbar air encephalography and bilateral carotid angiography were performed. No significant abnormalities were noted. Studies of carbohydrate metabolism showed that after an oral dose of 50 g. of glucose the blood-sugar level rose to 140 mg. and then fell to 40 mg. per 100 ml., remaining low for four hours. During this time the rectal temperature progressively fell to 92·4° F (Fig. 6).

In periods of hypothermia it was found that the patient excreted a large volume of dilute urine at night, and that her temperature, though subnormal, was usually higher in the morning than in the evening. It thus appears that

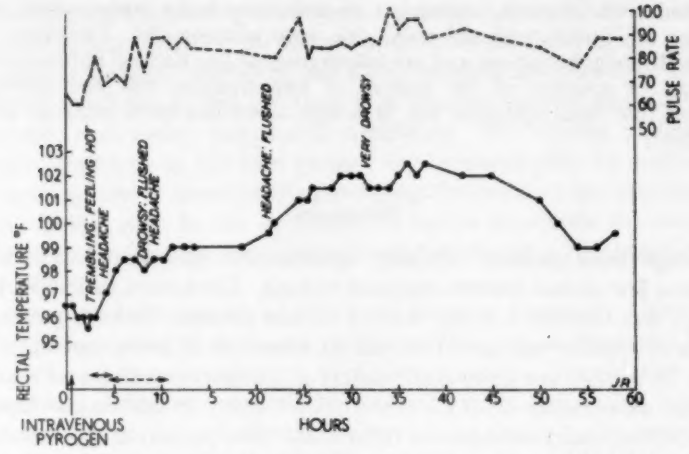

FIG. 5. Case 2. Effect of intravenous pyrogen on the pulse-rate and rectal temperature.

←——→ Period of expected maximum response to pyrogen in a normal subject.

←——→ Expected duration of fever after maximum response.

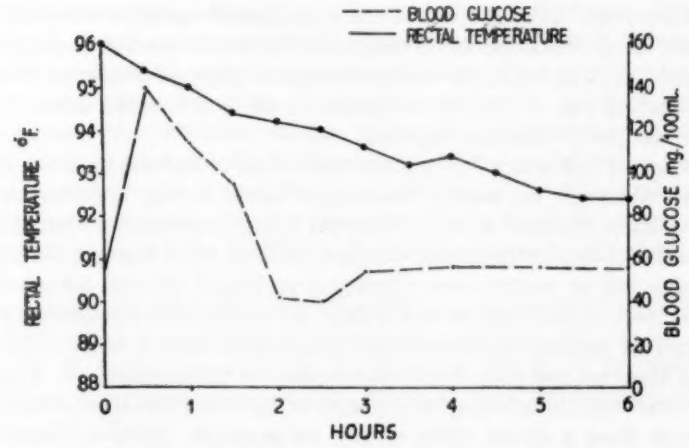

FIG. 6. Case 2. Prolonged glucose tolerance test and rectal temperature after 50 g. oral glucose.

there was a reversal of the diurnal rhythm of temperature and urine formation. During several episodes of hypothermia there was evidence of loss of weight associated with diuresis. Attempts to influence body temperature by the induction of diuresis with chlorothiazide were unsuccessful. Prolonged treatment with phenobarbitone and tri-iodothyronine has had no influence on the frequency or severity of the attacks of hypothermia, but the patient has remained free from epileptic fits, although there has been some mental deterioration.

Discussion

Although both patients exhibited spontaneous episodes of hypothermia, there were few clinical features common to both. The second patient had frank epilepsy, and the first a family history of this disease. In both patients the episodes of hypothermia have recurred for a number of years, especially in the winter. In neither was there good clinical or laboratory evidence of a primary endocrine abnormality or of an encroaching lesion. In addition to their sex, they exhibited many conspicuous differences. The pattern of the attacks was very dissimilar. The man had repetitive daily episodes of hypothermia lasting some hours, and associated with sweating and prostration. The girl developed sustained hypothermia for days or weeks on end. Transient mental retardation occurred in the man only at the depth of the bouts of hypothermia, but some permanent mental deterioration has developed in the girl. In many important respects the man resembles the patients described by Hines and Bannick (1934) and by Hoffman and Pobirs (1942). In both patients reported by these authors the incidence and daily pattern of the hypothermic episodes were similar to those seen in our first case. In all three men the attacks started in childhood or early adult life, and continued for years without physical or mental deterioration. Sweating was a conspicuous feature in all, and in none was a primary cause or associated disease recognized.

In respect of laboratory findings also there were differences between our two patients. Although the fasting blood-sugar levels during hypothermia were normal in both, thus excluding spontaneous hypoglycaemia, the man exhibited a rise in blood-sugar level as the temperature fell, while the girl developed a progressive fall in temperature (during a prolonged glucose tolerance test) when the blood-sugar level also was falling. When hypothermic the first patient had impaired glucose tolerance; and, although he has a family history of diabetes, there are two more likely explanations of this impairment. Disturbed carbohydrate metabolism may be a feature of hypothalamic disease itself, or it may result from a direct effect of low temperature. Thus an inability to utilize glucose may be due to the inhibition of insulin or of hexokinase by cold (Laufman, 1951; Vandam and Burnap, 1959).

The response to pyrogenic material given intravenously differed in our two patients. The man exhibited a response that was in every respect normal, except that it occurred when the temperature had still not risen to a normal level. This result suggests that, although his temperature-regulating mechanism

was working normally, it was set at a lower level than normal. This interpretation is supported by the results of the body-warming test. In the second patient there was evidence that during the attacks the temperature-regulating mechanism was not acting normally, for there was an excessive delay in the response to intravenous pyrogen. Moreover, the rise in temperature caused by external heating was much less in this girl than that reported by Davison (1940) in a hypothermic man under comparable conditions. The finding of increased adrenergic sensitivity in the first patient may perhaps offer an explanation for the development of atrial fibrillation during the depth of the hypothermia. Atrial fibrillation may be the expression of undue sensitivity to circulating adrenaline. Similar hypersensitivity has been described in hibernating animals (Kayser, 1957).

The cause of intermittent hypothermia remains uncertain. Hines and Bannick (1934) attributed their case to encephalitis, and Hoffman and Pobirs (1942) attributed theirs to epilepsy. The clinical entity of diencephalic autonomic epilepsy was first suggested by Penfield (1929), but in his patient a tumour, thought to be a cholesteatoma, was later shown to be responsible. Our first case, and those described by Hines and Bannick and by Hoffman and Pobirs, perhaps qualify to be described as diencephalic autonomic epilepsy better than that originally described by Penfield. In all three the long duration of the condition (up to 20 years), and the absence of deterioration, seemed to exclude a progressive lesion such as a tumour.

In our second patient there is less reason to exclude a focal lesion. Although air encephalography and cerebral arteriography gave normal results, there could still be a small focal degenerative lesion of the hypothalamus. Engel and Aring (1945) described a patient with hypothalamic attacks, in this instance with pyrexia, extending over many years, and later shown to be due to such a lesion. In none of the four cases of periodic hypothermia has there been any other evidence of hypothalamic disease, such as diabetes insipidus, disturbance of sleep, or hypogonadism. From this we may infer that the lesion, whatever it is, is extremely localized, restricted, and selective. By analogy with pyrexia, spontaneous hypothermia may be classed as intermittent or remittent, and exemplified respectively by the first and second patients here reported.

We are indebted to Professor C. H. Stuart-Harris and Professor D. V. Hubble, under whose care the patients were originally admitted; and to Dr. K. E. Cooper, Dr. S. P. Meadows, Dr. W. B. Matthews, Mr. R. H. Shephard, and Dr. D. Marrack for their special studies. Sister L. Edwards provided valuable assistance with Case 2.

Summary

A description is given of two young adults who exhibited over a number of years periodic reductions in body temperature. In neither instance was there evidence of an endocrine or other recognized cause. Reference is made to two

previously described cases of periodic hypothermia, and the possible cause of the disturbance is briefly discussed.

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DISTAL TUBULAR FUNCTION IN CHRONIC HYDRONEPHROSIS[1]

By G. M. BERLYNE

(From the Department of Medicine, Manchester Royal Infirmary)

CHRONIC hydronephrosis is a common condition in the adult, and would be expected to result in damage to the collecting and distal convoluted tubules. Little work has been published on distal tubular function in adults with obstructive disease of the renal tract, although some investigations have been carried out in infants and children with hydronephrosis (Ericsson, Winberg, and Zetterström, 1955; Earley, 1956; Zetterström, Ericsson, and Winberg, 1958; Winberg, 1959). The purpose of the present paper is to record the results of investigation of distal tubular function in seven patients with chronic hydronephrosis, six of whom were adults, and to stress the common occurrence of clinically important disturbances of renal function in such patients. The case histories are given in the Appendix.

Investigations

The investigations employed were designed to assess the following distal tubular functions: concentrating ability under pitressin stimulation, acidification, ammonia production, total hydrion excretion, and T^cH_2O.

1. *Concentrating ability.* After intramuscular injection of five units of pitressin tannate in oil, consecutive hourly specimens of urine were collected for four to six hours, and the maximum osmolality was determined. The pitressin tannate was shaken well and was in fine suspension in the oil before it was injected, each injection being given by the author.

2. T^cH_2O is defined as $C_{osm}-V$ under conditions of pitressin stress and mannitol diuresis, where $C_{osm} = U_{osm}V/P_{osm}$; U_{osm} = urine osmolality; P_{osm} = plasma osmolality; and V = urine excreted in ml. per minute. It was determined by the method of Cohen, FitzGerald, Fourman, Griffiths, and de Wardener (1957) for their Case 2.

3. *Acidification.* The test of Wrong and Davies (1959) was used, ammonium chloride being given in a dosage of 0·1 g. per kg. of body weight in all non-acidotic patients. If the patient was already acidotic, several timed urine specimens were examined for pH and ammonia excretion. An aliquot portion

[1] Received January 18, 1961.

of the urine of every patient was incubated for one to two hours at 37° C, urea and ammonia content being determined before and after incubation: absence of change of concentration of urea and ammonia was taken to indicate the absence of significant numbers of urea-splitting organisms in the urine. In patient 7, in whom there was a large bladder due to unrelieved prostatic obstruction, the acidification test was modified so as to compensate for the large volume of urine in the bladder (about 1 litre): after loading with 7 g. of ammonium chloride according to the scheme of Wrong and Davies (1959), a further 3 g. of ammonium chloride were given three hours later, followed by two doses of 2 g. at intervals of 10 hours, for a total of 24 hours. During this time 6·184 litres of urine were passed, the plasma CO_2 level being depressed to 20·2 m-moles per litre or less throughout the period of acidification. Glomerular filtration rate was determined by standard methods of inulin and endogenous creatinine clearance.

Chemical methods used were as follows:

Sodium and potassium	E.E.L. flame photometer.
Plasma CO_2	Van Slyke manometric apparatus.
Osmolality	Fiske cryoscopic apparatus.
Inulin	Bacon and Bell (1948).
Urinary creatinine	Bonsnes and Taussky (1945).
Serum creatinine	Roscoe (1953).
Ammonia	Conway microdiffusion technique.
Urea	'Autoanalyser'.
Titratable acidity	Wrong and Davies (1959).
Urinary pH	Marconi pH-meter and glass electrode.

Results (Tables I, II, and III)

1. *Acidification test*

(i) *pH of urine* (Fig. 1). Six out of seven patients with chronic hydronephrosis were unable to acidify their urine adequately according to the criteria of Wrong and Davies (1959). Normal persons can reduce the urine pH below 5·3 after taking 0·1 g. of ammonium chloride per kg. One patient (No. 2) was already so acidotic (plasma CO_2 14·1 m-moles per litre) that no oral loading was necessary, yet she produced a constantly alkaline urine of pH 7·04 on repeated testing. In Case 7 there was an unrelieved urinary obstruction, resulting in chronic retention with a residual urine volume of about one litre: in order to exclude the buffering effect of the residual urine on the pH of the urine passed during acidification, the test of Wrong and Davies was modified by the addition of small doses of ammonium chloride so that a persistent acidosis was maintained for 24 hours. During this time 6·18 litres of urine were passed, yet the pH remained at 6·10, indicating inability to acidify. Five weeks later (four weeks after the obstruction was relieved by prostatectomy) the patient could acidify the urine normally to pH 5·06. Patient 4, two months after relief of the obstruction, could just achieve a normal urine pH of 5·3.

(ii) *Ammonia excretion* (Fig. 2) was reduced in five out of six patients on testing initially. In Case 4, on repetition of the ammonium chloride loading two months after prostatectomy, ammonium excretion was still below normal, but appreciably higher than on the previous test carried out before the obstruction was relieved. In Case 7 bladder emptying was so variable that no attempt could be made to determine ammonia excretion before prostatectomy. One

TABLE I

Clinical Features and Concentration Test in Chronic Hydronephrosis

Case number	Age (years)	Sex	Cause of chronic bilateral hydronephrosis	Previous urinary infection	Urea-splitting organism at time of test	Maximum urinary osmolality (m-osmoles/kg.)	Glomerular filtration rate (ml./min.) C_{inulin}	$C_{creatinine}$
1	53	Male	Periureteric fibrosis	Yes	Absent	309	25·7	20·2
2	53	Female	Aberrant renal vessels	Yes	Absent	341	9·0	..
3	11	Male	Bladder-neck obstruction	Yes	Absent	268	28·6	20·0
4	64	Male	Benign prostatic hypertrophy	No	Absent	439	..	31·2
5	15	Female	†Neurogenic	Yes	Absent	265	37·5	..
6	37	Male	†Neurogenic	No	Absent	680	..	64
7	67	Male	Benign prostatic hypertrophy	No	Absent	264* / 486†	..	13·7‡ / 65·0†

* At a time when serum osmolality was 343 and urinary obstruction unrelieved.
† Four weeks after relief of obstruction.
‡ Calculated from mean of two 24-hour creatinine clearances.

TABLE II

Acidification Test and Serum Electrolytes in Chronic Hydronephrosis

Case number	Minimum urinary pH after ammonium chloride	Maximum urinary ammonia excretion μ-equiv./min.	Range of urinary ammonia concentration m-equiv./l.	Maximum total H^+ excretion ($NH_4^+ + TA - HCO_3^-$) μ-equiv./min.	Serum Na^+ m-equiv./l.	Serum K^+ m-equiv./l.	Serum HCO_3^- m-equiv./l.	Blood urea mg./100 ml.
1	6·38	31·2	23·1–14·6	36·1	144	5	24·8	90
2	7·04	20·2	20·4–18·0	..	140·6	6·3	14·1	121
3	5·77	14·0	4·7–4·0	33·4	138	4·5	19·5	96
4	5·46* / 5·30†	15·0 / 19·6	9·8–4·0 / 11·5–8·1	28·1 / 41·4	137 / 139·9	4·5 / 4·65	27·2	95 / ..
5	5·66	29·0	14·0–11·8	44·9	138·1	4·54	28·2	54
6	5·10	34·0	23·6–12·1	68·6	140	4·5	28·4	22
7	6·10* / 5·01‡	.. / 32·0	.. .. / 9·0–18·2	.. / 65·2	158·4 / 137	4·7 / 5·2	29·4 / ..	78 / 23

* Before prostatectomy. † 2 months after prostatectomy. ‡ 1 month after prostatectomy.

month after the operation the urinary excretion of ammonia was still low. In Cases 2, 3, and 5 the ammonia *concentration* in the urine was fairly constant, increases in ammonia excretion being mainly determined by the rate of urine flow.

(iii) *Titratable acidity* (Fig. 3) was measured usually as titratable acid (TA)—HCO_3^- in urine with a pH above 6·0. Titratable acidity measured directly was below normal in Case 5 and normal in Case 6 (the patient who could acidify the urine normally). Titratable acidity was normal in Case 7 after relief of the obstruction.

(iv) *Total hydrion excretion* ($NH_4^+ + TA - HCO_3^-$) (Fig. 4). In four cases out of five the total hydrion excretion was reduced. In patient 6 excretion was normal. Patient 7 was unsuitable initially for accurate timed collections. Patient 4 showed improvement in hydrion excretion two months after the urinary obstruction was relieved, although the results were still below normal. Patient 7, one month after prostatectomy, had a normal total hydrion excretion.

TABLE III

Determination of T^cH_2O in Chronic Hydronephrosis

Minutes from commencement of controls	*Urine minute volume (ml./min.)*	*Urine osmolality (m-osmoles/kg.)*	*Serum osmolality (m-osmoles/kg.)*	C_{osm} *(ml./min.)*	T^cH_2O $(C_{osm} - V)$ *(ml./min.)*
Case 2					
Mannitol and pitressin drip commenced at zero minutes					
10	empty bladder and reject				
30	2·8	377	..	3·29	+0·49
50	3·55	371	321	4·11	+0·56
70	4·0	362	..	4·51	+0·51
90	4·8	359	325	5·32	+0·52
110	4·8	360	..		
				T^cH_2O maximum value	+0·56
Case 3					
0	3·8	248	..	3·46	−0·34
5	10·6	250	272	9·7	−0·90
5	Intravenous mannitol and pitressin started				
60	2·1	268	295	1·9	−0·20
80	2·4	260	..	2·15	−0·25
105	1·92	261	..	1·65	−0·27
117	..	..	303	..	..
135	2·23	266	..	1·96	−0·27
				T^cH_2O maximum value	−0·20
Case 5					
Mannitol and pitressin started at zero			270	..	..
30	reject	..	..	..	..
50	4·65	240	..	4·0	−0·65
56	..	..	275	..	..
71	4·37	236	280	3·73	−0·64
90	6·37	234	281	5·37	−1·0
105	8·0	231	..	6·57	−1·43
120	8·67	229·5	..	7·07	−1·60
135	7·15	229	..	5·85	−1·30
150	5·8	236	..	4·97	−0·9
210	5·25	209	..	4·07	−1·2
270	5·67	204	..	4·28	−1·4
				T^cH_2O maximum value	−0·64

2. *Response to pitressin and determination of T^cH_2O*

In three out of seven patients the maximum urine osmolality, after 5 units of pitressin tannate given intramuscularly, remained well below that of plasma. In Case 7 the maximum urine osmolality after pitressin was 264 m-osmoles per kg., at a time when plasma osmolality had been 343 m-osmoles per kg. for several days, the serum sodium being 158 m-equiv. per litre owing to insufficient fluid intake. In two of the three patients with obligatory urinary hypotonicity T^cH_2O was determined, and was found to have a negative value in both

patients; a similar result was obtained by Cohen, FitzGerald, Fourman, Griffiths, and de Wardener (1957) in a patient with obligatory hyposthenuria due to hyperparathyroidism. T^cH_2O was not determined in Case 7, because of the technical impossibility of employing clearance techniques in the presence

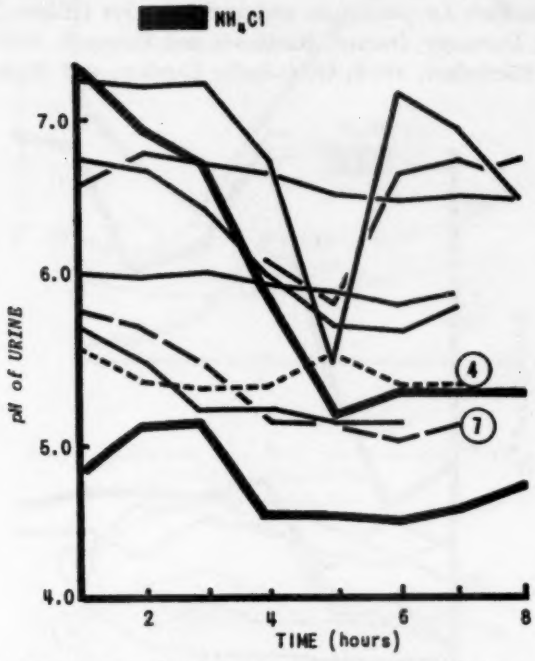

FIG. 1. Urine pH during the ammonium chloride test.
Bold lines indicate the upper and lower limits of normal of Wrong and Davies (1959).
Thin continuous lines represent the results in patients with chronic hydronephrosis.
Interrupted lines indicate the results in patients with chronic hydronephrosis after operation.
Ammonium chloride was given in a dosage of 0·1 per kg.

of unrelieved urinary obstruction. In patient 2, who could concentrate to 341 m-osmoles per litre, T^cH_2O was +0·49 ml.; if corrected for the low glomerular filtration rate, T^cH_2O per 100 ml. of glomerular filtrate would have been 5·45 ml. per minute—a normal figure. Thus patients with chronic hydronephrosis can be divided into three groups:

(*a*) Those who can concentrate normally (one patient; Case 6).

(*b*) Those who have an obligatory hyposthenuria and a negative T^cH_2O, and have nephrogenic diabetes insipidus (three patients).

(*c*) Those in whom concentration is impaired in association with the reduction of glomerular filtration, and in whom T^cH_2O per 100 ml. of glomerular filtrate may be in the normal range (three patients).

Discussion

The functions of the distal convoluted tubules and the collecting tubules include acidification of the urine, production of concentrated urine under the influence of antidiuretic hormone, addition of ammonia to the urine, and ion exchange of sodium for potassium and hydrogen ion (Hilger, Klümper, and Ullrich, 1958; Darmady, Durant, Matthews, and Stranack, 1960; Pitts, Gurd, Kessler, and Hierholzer, 1958; Gottschalk, Lassiter, and Mylle, 1960). The

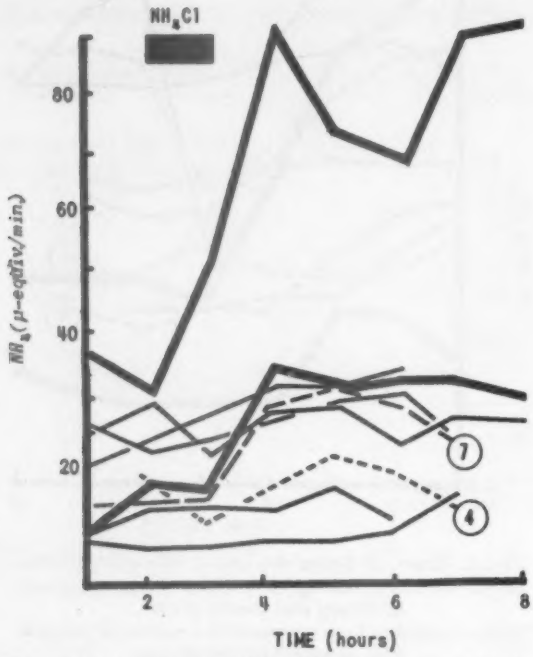

FIG. 2. Ammonia excretion after ammonium chloride loading.
Key as in Fig. 1.

most complete studies of function in chronic hydronephrosis have been carried out in infants and children by Ericsson, Winberg, and Zetterström (1955), Zetterström, Ericsson, and Winberg (1958), and Winberg (1959). In the first paper of Ericsson, Winberg, and Zetterström (1955) only one infant was subjected to an acidification test (with calcium chloride); the urinary pH did not fall below 6·6. One patient was given pitressin, after which the urinary specific gravity fell to 1,009 from 1,015, the highest spontaneous reading. In 1958 Zetterström, Ericsson, and Winberg published details of two further cases of infantile hydronephrosis (one of which had been reported earlier), in which the function of each kidney was tested separately. In both patients the markedly hydronephrotic kidney was unable to acidify in response to an acid load. A

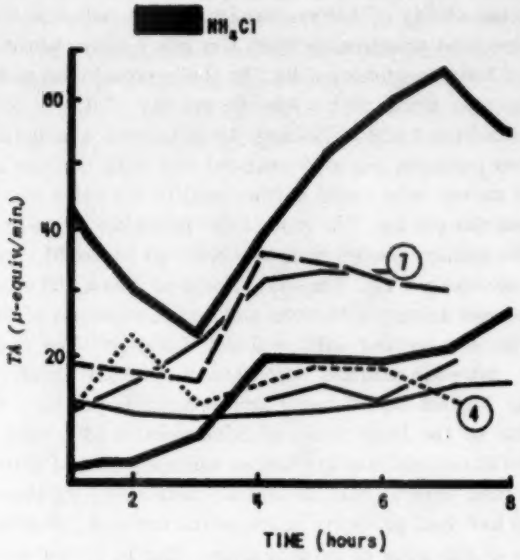

FIG. 3. Titratable acid (TA) excretion during the ammonium chloride test.
Key as in Fig. 1.

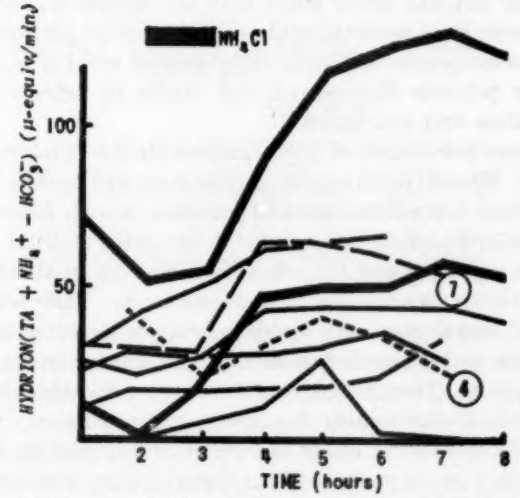

FIG. 4. Total hydrion excretion during the ammonium test.
Key as in Fig. 1.

pitressin test in one patient yielded pyelostomy urine from the severely affected kidney with an osmolality of 150 m-osmoles per kg., whereas the urine voided from the bladder (and presumably from the less hydronephrotic kidney) had an osmolality of 350 m-osmoles per kg. In their second case water deprivation produced pyelostomy urine with a specific gravity of 1,013, bladder urine at the same time reaching 1,029. Winberg (1959) carried out distal tubular function tests on two patients, one a 13-year-old boy with chronic hydronephrosis due to urethral valves, who could neither acidify his urine nor concentrate it above 150 m-osmoles per kg. The glomerular filtration rate was normal. Four months after the urinary obstruction was relieved he could concentrate urine to over 400 m-osmoles per kg. The second patient was a girl of nine and a half years, with repeated urinary infections and hydronephrosis of probable neurogenic origin, who was treated with catheter drainage. She had no acidification test, but pitressin-tannate stimulation yielded urine with variable osmolalities, the highest figure being 280 m-osmoles per kg.; the variability was possibly due to the large residual urine volume (300 ml.). Drainage for six days resulted in osmolalities in random urine samples of 370 m-osmoles per kg. Winberg's first patient had no urinary infection; all the other patients from this group had had previous instrumentation and infection, but had no active infection at the time of investigation. Earley (1956) carefully investigated a five-month-old boy with bilateral hydronephrosis due to chronic inflammatory tissue obstructing the bladder neck; he had had repeated urinary-tract infections, the first commencing at the age of six weeks. The maximum urinary specific gravity was 1,004 after adequate pitressin administration. Urinary pH was never lower than 6·3 despite a mild acidosis, the plasma bicarbonate level never rising above 22·5 m-moles per litre. The patient was not given an exogenous acid load. After surgical relief of the urinary-tract obstruction the polyuria disappeared, but details of urinary concentrating ability at that time were not recorded.

There have been few reports of renal function studies in adults with chronic hydronephrosis. Edvall (1959) suggested that there had been no studies in the adult, and confined himself to studies of proximal tubular function. Roussak and Oleesky (1954) described two cases of nephrogenic diabetes insipidus, one due to multiple myeloma and the other to carcinoma of the prostate gland causing distal tubular damage due to hydronephrosis. Their second case was well documented, and showed early hydronephrosis on intravenous pyelography. Hypertonic saline and pitressin produced a maximum urinary osmolality of 258 m-osmoles per kg. Three grammes of ammonium chloride gave a maximum urinary pH of 6·0. Unfortunately this dosage is approximately half that used by Wrong and Davies (1959), and it is difficult to interpret the significance of the result, especially in the presence of unrelieved urinary obstruction (compare Case 7 in the present paper, in which acid loading was maintained for 24 hours to overcome the buffering effect of the residual urine). In their first case, however, Roussak and Oleesky found that acid urine could be produced (pH 5·0), although concentrating ability was much reduced. Morgan, Forrest, and Lowe

(1955) described a case of hydronephrosis due to carcinoma of the prostate, with a urinary specific gravity below 1,007, resistant to pitressin, rising to 1,014 after relief of the obstruction; acidification was not carried out. Knowlan, Corrado, Schreiner, and Baker (1960) reported three cases of periureteric fibrosis, in one of which the patient passed five to seven litres of urine a day: although they described this case as 'diabetes-insipidus like', the patient was

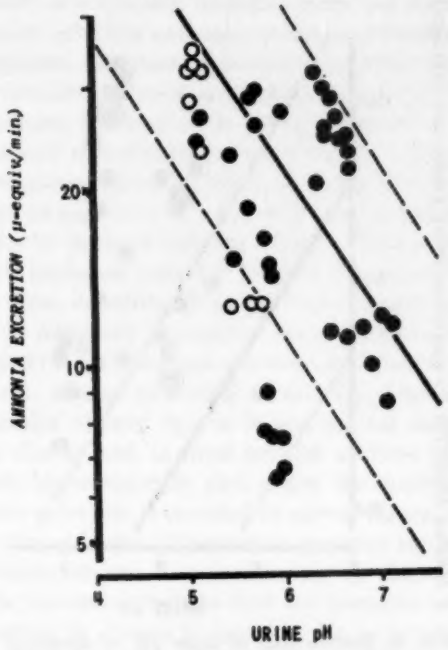

FIG. 5. Relationship of ammonia excretion to urine pH.
The ordinate scale is logarithmic. Open circles represent results in Case 7 after operation.
The bold line is the mean, and interrupted lines the 95 per cent. confidence limits, of the normal supplied by Wrong (personal communication).

able to concentrate urine to a specific gravity of 1,013 on fluid deprivation, the maximum urine osmolality being 429 m-osmoles per kg. at a time when plasma osmolality was 318 m-osmoles per kg. The ratio of urine to plasma osmolality after pitressin was 1·35, which clearly proved that the patient did not have nephrogenic diabetes insipidus. His spontaneous urinary pH was 5·0, which indicates normal ability to acidify. In the other two cases the urinary specific gravity could rise to 1,013 and 1,020 respectively; the urinary pH is not recorded. Mees (1960) described a patient with polyuria and hydronephrosis, but gave no details of urinary concentrating power in the water-losing phase. Acidification tests were not reported.

The reversibility of the distal tubular lesion has been demonstrated with respect to two functions. First, *concentrating ability*: Winberg's (1959) first patient recovered concentrating ability after four months, as did the second patient of Roussak and Oleesky (1954). Earley's (1956) patient had polyuria which cleared up after operation. Our seventh patient could concentrate urine only to 486 m-osmoles per kg. Secondly, *acidification*: this function was found

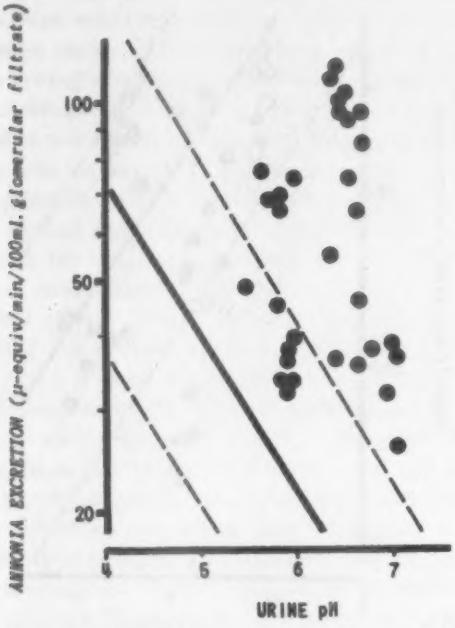

FIG. 6. Relationship of urine pH to ammonia excretion corrected for reduction in glomerular filtration rate.
Key as in Fig. 5.

to be normal in Cases 4 and 7 of the present series after relief of urinary obstruction, whereas it had been impaired beforehand. In none of the other patients was a second test of acidification possible, usually because of the difficulty of curing hydronephrosis in the absence of an obvious cause. The condition of patient 1, when last heard of, was unchanged; but he abhorred venepuncture and did not wish further investigation.

The output of ammonia was found to be low in five out of six cases when compared with that found in normal persons after an ammonium chloride load, and was normal or low in relation to the pH of the urine (Fig. 5). Similar findings were reported by Reynolds (1958) and Wrong and Davies (1959) in renal tubular acidosis. Similarly, as in renal tubular acidosis, in six out of seven cases the total hydrion excretion was reduced. In contrast, our patients 1, 4, 5, and 6 had no systemic acidosis, which makes their condition similar to the

three cases reported by Wrong and Davies (1959) as 'incomplete renal tubular acidosis'. In their cases there was inability to acidify the urine in the absence of a systemic acidosis; all three patients had nephrocalcinosis, but it should be remembered that they came to notice in the investigation of cases of nephrocalcinosis. In our experience this syndrome of incomplete renal tubular acidosis is not confined to nephrocalcinotic patients, because inability to acidify the urine in the absence of a systemic acidosis occurs not only in chronic hydronephrosis but also in calculous and non-calculous pyelonephritis (Berlyne, unpublished observations). It seems reasonable to attribute this syndrome of incomplete renal tubular acidosis to isolated damage to the distal and collecting tubules with continuing function of the proximal tubules. Two of Wrong and Davies's three patients with incomplete renal tubular acidosis had a very high level of urinary ammonia excretion, which was absent in our patients.

Can the findings be explained in terms of Platt's hypothesis (1952) that the functional changes in diseased kidneys are due simply to reduction in the number of effective nephrons present? Bricker, Morrin, and Kime (1960) have amplified Platt's view, describing it as the 'intact nephron hypothesis'. Ammonia excretion in advanced generalized renal disease and in renal tubular acidosis is depressed; if the ammonia excretion is corrected for the low glomerular filtration rate, and so expressed as micro-equivalents per minute per 100 ml. of glomerular filtrate, figures in the normal range are obtained in generalized renal disease and in renal tubular acidosis (Wrong and Davies, 1959). In chronic hydronephrosis also, when the results are so expressed, depressed ammonia excretion is elevated to normal figures relative to the acid load given. Thus the reduction of ammonia excretion in the majority of cases of chronic hydronephrosis can be accounted for by the reduction in effective renal tissue. It is interesting to note that the excretion of ammonia relative to urine pH is normal in chronic hydronephrosis, as in renal tubular acidosis (Reynolds, 1958; Wrong and Davies, 1959); if ammonia excretion is corrected for the reduction in glomerular filtration rate, it will be seen that the corrected ammonia excretion is even higher than normal in chronic hydronephrosis (Fig. 6); this also occurs in renal tubular acidosis (Wrong and Davies, 1959). The defect in concentration can also be considered to be partly explained by the 'intact nephron hypothesis' if the data in Case 2 are examined; T^cH_2O was reduced in this patient but, when expressed as ml. per minute per 100 ml. of glomerular filtrate, fell within normal limits. It is more difficult to see how negative values of T^cH_2O (which were found in two of our patients with renal diabetes insipidus) can be explained by Platt's hypothesis, because of the mathematical difficulty introduced by negative values of T^cH_2O, which must indicate insensitivity of the concentrating mechanism to antidiuretic hormone; in these patients, with obligatory urinary hypotonicity, the concentrating defect presumably reflects damage to all nephrons, and not only a reduction in the number which are working. Similarly, inability to lower urinary pH appears to be a specific qualitative defect in chronic hydronephrosis, as in renal tubular acidosis. In summary, the reduction in ammonia excretion in chronic hydro-

nephrosis is probably due to the reduction in the number of effective nephrons; the reduction in concentrating power is sometimes due also to this reduction, and sometimes a qualitative change affecting all tubules; the defect in lowering urinary pH is due to a qualitative change affecting the tubules, and is independent of reduction in renal mass.

Inability to concentrate the urine giving rise to nephrogenic diabetes insipidus occurred in three of the patients in the present series. In two of these patients, in whom measurement of T^cH_2O was made, obligatory urinary hypotonicity was associated with a negative value of T^cH_2O; this finding also occurred in a polyuric patient with hyperparathyroidism investigated by Cohen, FitzGerald, Fourman, Griffiths, and de Wardener (1957). Hypokalaemic nephropathy can likewise lead to pitressin-resistant polyuria with all the features of renal diabetes insipidus; the resultant thirst, for example, is a prominent symptom in hypokalaemic nephropathy due to primary aldosteronism. Carone and Epstein (1960) have recently described a patient with a nephrogenic type of diabetes insipidus in whom microdissection of the kidneys revealed amyloid deposits in the distal convoluted and collecting tubules. Occasionally nephrogenic diabetes insipidus is a congenital anomaly, appearing in male subjects with a sex-linked recessive mode of inheritance (Dancis, Birmingham, and Leslie, 1948). None of our patients had any evidence of hypercalcaemia, hypokalaemia, amyloid disease, or congenital nephrogenic diabetes insipidus.

The presence of infection in the urinary tract is very common in obstructive lesions, especially after the instrumentation necessary for diagnosis and therapeutic purposes, and the resultant pyelonephritis may cause defects in acidification and concentration (Kleeman, Hewitt, and Guze, 1960). In Cases 4 and 7 of the present series there was no urinary-tract infection at the time of the initial tests, nor, as far as could be ascertained, had there been one in the past; abnormal results were obtained on both acidification and urine concentration tests. Similarly, in Winberg's (1959) Case 1, the patient had no renal infection at the initial finding of hyposthenuria and inability to acidify the urine: it is therefore established that true hydronephrosis alone, without clinical evidence of pyelonephritis, can cause defects in distal tubular function. In studies in dogs Kerr (1954) found that induction of unilateral hydronephrosis caused diminished concentrating ability on the affected side, but acidification was unimpaired.

The response of chronic hydronephrotic kidneys to sudden relief of urinary-tract obstruction has been investigated by Wilson, Reisman, and Moyer (1951) in three patients, in one of whom the balance of both sodium and water was measured; this patient lost 53 g. of sodium ion in cumulative balance by the fourth day after relief of his urinary obstruction; the cumulative loss of water in the same period was approximately 40 litres. Unfortunately data for the calculation of urine osmolality were not given, nor was the acidifying ability tested. Parsons (1954) again noted massive loss of salt and water on relief of urinary obstruction, and Bricker, Shwayri, Reardan, Kellog, Merrill, and

Holmes (1957) further investigated this problem. In the three cases of the present series in which obstruction was relieved there was no abnormal loss of salt in the urine.

In patients with chronic hydronephrosis the presence of acidosis and diminished ability to acidify the urine may call for the cautious administration of sodium and potassium citrate, as in renal tubular acidosis. Adequate fluid should be given to all patients with obligatory urinary hypotonicity to prevent their becoming dehydrated; patient 7 developed a serum osmolality of 343 m-osmoles per kg., due to lack of adequate drinking because he despaired of quenching his thirst. Nevertheless, after dehydration and acidosis have been corrected, if possible the obstruction should be relieved surgically without delay, in the hope that the lesion of the distal and collecting tubule may be reversible (see Cases 4 and 7 of the present series, Case 2 of Roussak and Oleesky (1954), Case 1 of Winberg (1959), and probably those of Earley (1956) and Mees (1960)).

I wish to thank Professor D. A. K. Black for his advice and helpful criticism; Mr. Thomas Moore for allowing me to investigate his patients; Dr. Oliver Wrong for supplying me with data of the normal ammonia excretion/urinary pH relationship; the Department of Medical Illustration, Manchester Royal Infirmary, for the diagrams; and Mrs. Margaret Dyson for technical assistance.

APPENDIX

Case 1. N. G., a 54-year-old man, was seen with a left-sided scrotal swelling in August 1959; this was thought to be possibly a varicocoele, and intravenous pyelography was carried out to exclude a renal tumour; instead, an inactive left kidney was found. On left retrograde pyelography clubbed calyces were seen. A hydrocele was excised. Four months later he complained of anorexia and loss of weight, culminating in inability to pass urine; formerly his only urinary symptom was having to pass urine twice at night. On examination his bladder was not enlarged, the prostate being normal. His blood-pressure had risen to 200/140 from its usual 145/85. Catheterization of the bladder produced no urine, and after bilateral ureteric catheterization right nephrostomy produced a flow of clear urine. A pyelostomy tube was inserted. His blood urea fell from 168 mg. to 88 mg. per 100 ml. on 5.4.60; two days later laparotomy was performed by Mr. T. Moore, who found the right ureter to be compressed by periureteric fibrosis. This diagnosis was later confirmed histologically by biopsy, and the ureter was freed throughout its length. The patient made an excellent recovery, urine being passed *per urethram* and the pyelostomy closed. Three months later his blood urea was 40 mg. per 100 ml., and the blood-pressure was normal.

Case 2. I. G., a 53-year-old housewife, was found to have chronic myeloid leukaemia in November 1959. In addition she was found to have two large cystic masses in the abdomen, and had developed frequency of micturition together with nocturia. Her blood-pressure was 175/96. She was thin and pale. Intravenous pyelography failed to outline any kidney shadows, and her blood urea was found to be 156 mg. per 100 ml.; urea clearance was 7 to 15 per cent.

of normal. A catheter specimen of urine was sterile. The maximum urinary specific gravity after overnight deprivation of fluid was 1,008. Retrograde pyelography showed obstruction at the uretero-pelvic junction. At cystoscopy indigo carmine first appeared at the left ureteric orifice 25 minutes after intravenous injection; none had appeared at the right ureteric orifice in 30 minutes. On 2.1.60 a left nephrostomy was made, urine being released under pressure. The serum bicarbonate was 14·7 m-equiv. per litre on 8.1.60, and a coliform organism was cultured from the nephrostomy urine at this time. Retrograde pyelography showed that the kidney pelvis did not fill. At operation on 17.2.60 a large right hydronephrosis (caused by a leash of aberrant veins at the pelvi-ureteric junction) was found; it contained 2 to 3 litres of urine. In spite of plication and removal of the obstruction, no function was restored to the right kidney. The blood urea remained high; at this time the patient underwent tests of distal tubular function. After pyeloplasty on 19.5.60 the patient died from bleeding at the site of operation.

Case 3. R. L., an 11-year-old boy, had developed bladder-neck obstruction, bilateral hydronephrosis, and chronic urinary retention in infancy; this was treated by bladder-neck resection. On admission he complained of incontinence of urine for as long as he could remember. His bladder was intermittently palpable above the pubis. The blood-pressure was 115/75. Residual urine amounted to 240 ml. Cystoscopy showed that the bladder was trabeculated; the right ureteric orifice was normal. The blood urea was 116 mg. per 100 ml., and intravenous pyelography was not satisfactory. The bladder neck was resected on 28.8.60, after a transient urinary coliform infection following cystoscopy had been successfully treated with chloramphenicol. After operation his residual urine was only a few drops. The blood urea decreased to 97 mg. per 100 ml. on 8.8.60. His urinary incontinence subsided, and he had full control of micturition one month after operation, when tests of distal tubular function were done.

Case 4. J. L., a 67-year-old man, was admitted to St. Thomas's Hospital, Stockport, on 2.2.60 for paraphrenia of late onset. Physical examination disclosed that his bladder was enlarged up to the umbilicus; his prostate was small and firm. On direct questioning he said that he had noticed precipitancy for five years, and nocturia two to three times each night and hesitancy of micturition for two years. His urine was free from albumin and sugar, a random specimen having a specific gravity of 1,020. The blood urea was 67 mg. per 100 ml. Intravenous pyelography on 16.2.60 disclosed early bilateral hydronephrosis; after this investigation he became hypotensive and transiently anuric. A detailed report of this episode will appear elsewhere (Berlyne and Berlyne, in preparation). Nine days later he was transferred to Manchester Royal Infirmary, where he continued to make an uncomplicated recovery. An indwelling urethral catheter was inserted on 16.2.60 and decompression of the bladder carried out; the urine remained sterile for one month, during which time an acidification test was carried out (4.3.60), followed the next day by a pitressin-tannate test. Serum bicarbonate was 28·8 m-moles per litre at this time. Transurethral prostatectomy was performed on 22.3.60, benign prostatic hypertrophy being the histological diagnosis. The patient's blood urea decreased to 46 mg. per 100 ml., and he made a recovery complicated by a post-operative urethral stricture. A second acidification test was carried out two months after the first, and he has since had regular dilatation of the urethral stricture.

Case 5. V. H., a 15-year-old girl, was known to have developed frequency of micturition at the age of one year. She had had nocturnal enuresis all her life. She noticed that she always drank more than other members of her family, usually six to eight pints a day. At the age of 10 she was found on intravenous and retrograde pyelography to have bilateral hydronephrosis and hydroureter, the hydronephrosis gradually progressing for the next five years. During this time the blood urea varied between 26 mg. and 54 mg. per 100 ml. during the several periods she spent in hospital for urinary infections. On cystoscopy the bladder was normal, and a micturating cystogram showed considerable reflux. After overnight deprivation of water the urinary specific gravity rose to 1,004; two years later pitressin tannate gave a maximum specific gravity of 1,008. The patient was admitted to Manchester Royal Infirmary in August 1960 for investigation of renal function. Her blood-pressure was 100/65, and on physical examination she appeared normal. She was found to have pitressin-resistant diabetes insipidus, which was treated successfully with chlorothiazide, her glomerular filtration rate falling from 37 ml. to 17 ml. per minute with a decrease of urine volume from between 2·5 and 3 litres to 1,600 ml. a day. Further details of this case will be reported elsewhere (Stanbury and Berlyne, in preparation). The patient was found to have an asymptomatic staphylococcal infection of the urinary tract while in hospital.

Case 6. A 38-year-old bus driver complained of haematuria in November 1958. He was admitted to the Manchester Royal Infirmary under the care of Mr. T. Moore, and was found on cystoscopy to have a fibrous bar and trabeculated bladder. On ureteric catheterization a left hydronephrosis containing 220 ml. of urine was found. One year later he developed a left pyelonephrosis, which was drained. Two months after this operation intravenous pyelography showed the left kidney to be inactive; the right kidney was also hydronephrotic, with clubbed calyces and a dilated right upper ureter. Laparotomy on 8.2.60 disclosed some dilatation of the upper part of the right ureter, gradually narrowing into a normal ureter. There was no evidence of periureteric fibrosis. A left retrograde pyelogram had the appearance of an obstruction at the pelviureteric junction. The blood urea at this time was 31 mg. per 100 ml. *Staph. pyogenes* was grown on culture from several clean urine specimens. He was asymptomatic at the time of investigation.

Case 7. F. B., a 67-year-old plumber, developed hesitancy of micturition and nocturia in 1951, nine years before admission. The nocturia increased in frequency, and in 1954 he found that he was passing four pints of urine each night, and that the force of his urinary stream was poor. In 1957 he developed frequency of micturition by day, urinating at hourly intervals, and by March 1960 had developed precipitancy with occasional incontinence. Four months later his nocturia suddenly became worse; he had to pass urine seven times each night. At the same time he developed very severe thirst and a dry mouth. He was admitted in September 1960, under the care of Professor D. A. K. Black, to the Manchester Royal Infirmary, where he was found to have a blood-pressure of 195/135; his bladder was enlarged up to the umbilicus, and he had a very large prostate gland on rectal examination. His blood urea was 68 mg. per 100 ml., and serum sodium 150 m-equiv., chloride 104 m-equiv., and bicarbonate 29·4 m-equiv. per litre. The serum sodium one week later was found to be 156 m-equiv. per litre, and after another week 158·4 m-equiv. per litre. The serum osmolality at this time was 343 m-osmoles per kg., and the urine osmolality on the same day 264 m-osmoles per litre. He was passing three to four

litres of urine daily. His glomerular filtration rate (endogenous creatinine over a 24-hour period) was 12·5 and 15·5 ml. per minute on two consecutive days. He was given seven litres of water to drink daily; there was rapid amelioration of his thirst, and restoration of his serum electrolytes to normal. On 12.10.60 a suprapubic catheter was inserted into the bladder; the urine was sterile. One week later the urine osmolality rose to 372 m-osmoles per kg. after pitressin tannate; the patient underwent prostatectomy 10 days later. One month after operation he could acidify his urine; the blood urea was 23 mg. per 100 ml. The daily urine volume had fallen to between 1,200 and 1,500 ml., and his thirst and nocturia had disappeared. His blood-pressure had fallen to 100/70 on discharge.

Summary

Tests of distal tubular function were performed in seven cases of chronic hydronephrosis. Impairment of ability to acidify the urine was found in six out of seven. Obligatory urinary hypotonicity was present in three patients who had the clinical syndrome of nephrogenic diabetes insipidus; in three patients urinary concentrating ability was impaired, and in one it was unimpaired. In the patients who were unable to acidify the urine, ammonia production was low considering the acid load, but usually normal relative to the urinary pH. Two patients recovered acidifying ability, and one recovered concentrating ability, after the urinary obstruction was relieved.

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ENDEMIC FLUOROSIS[1]

With Particular Reference to Fluorotic Radiculo-Myelopathy

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With Plates 32 to 35

FLUORINE is placed at the head of the halogen group in the periodic table, and is one of the trace elements normally present in the body in very small amounts. It exerts a beneficial influence on the enamel of teeth. In certain circumstances, as by industrial exposure or excessive intake through drinking water, large quantities may be accumulated in the body, particularly in the bones. The latter type of chronic intoxication is designated as endemic fluorosis, and was first reported from India by Shortt, McRobert, Barnard, and Nayar (1937) and Shortt, Pandit, and Raghavachari (1937). Sporadic cases of this type of intoxication have been reported from Ceylon (Clark, 1942), China (Lyth, 1946), Argentina (Capizzaro, Paterson, Tolebo, Yigi, and Valotta, 1945), Japan (Dean and McKay, 1939), North Africa (Velu, 1933), Saudi Arabia (Tannir, 1959), the United States (Waldbott, 1960), and Europe (Benagiano, 1960). Although industrial fluorosis has been well described (Roholm, 1937), the clinical picture of endemic fluorosis is not so well known, particularly as regards its neurological complications. For these reasons we are reporting our experience of this disease for the last five years as seen in the Panjab, a northern state of India.

Patients Studied and Scope of Investigation

The present paper is based on a study of 60 cases observed from 1956 to 1960. The diagnosis in all cases was radiologically confirmed. There were 49 men and 11 women. Their ages varied between 28 and 80 years, with an average of 51 years. Most of the patients were active manual workers doing unskilled labour on farms, and living in the endemic area since birth; all had lived there more than 20 years. All were from a limited geographical area, mainly the Bhatinda and Sangrur districts of Panjab. This area has a fairly hot and dry summer, the temperature touching 47° C. This necessitates the drinking of a large quantity of water. The soil is sandy, and wells are the chief source of water supply for the population. The general standard of nutrition and living is very poor, and methods of sewage disposal very unhygienic. The area has been

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observed to have localized belts in which the subsoil water and the soil contain excessive quantities of fluorine, as high as 14 parts per million (p.p.m.) in some places.

Most of the cases were sporadic admissions to hospital, although a few patients were studied at the time of a field survey conducted in this area (Singh, Jolly, and Bansal, 1961). The cases were recorded on a special form, laying particular emphasis on the examination of teeth, goniometry, and the skeletal and nervous system. Roentgenograms of almost the whole of the skeleton were taken in every case. Besides the routine laboratory investigations, biochemical studies included blood estimations of urea, sugar, proteins, calcium, inorganic phosphorus, and alkaline phosphatase, and a detailed study of the cerebrospinal fluid wherever available. Fluorine was estimated by the thorium nitrate titration method in the blood, urine, and bone ash, and also in the water and soil samples. An open biopsy of the bone obtained from the tibia or iliac crest provided the material for histopathological studies and for fluorine estimation.

Observations

The symptomatology and the clinical picture in all advanced cases are remarkably similar, and it will be useful to illustrate the evolution of the disease and its neurological complications by a complete description of an advanced case which came to necropsy. This will be followed by an analysis of our observations.

Case 25. M. R., a 45-year-old male farmer, was admitted to hospital with the complaints of progressive weakness of all four limbs for the last eight years and incontinence of urine and stools for the last year. The complaints started insidiously with stiffness of the back and lower limbs, and occasional pains radiating from the back to the lower limbs. Weakness was first noticed in the right leg eight years before admission, followed by a similar weakness in the left leg after two years, so that the patient could not walk without support. About three years later the upper limbs were similarly affected. At this stage the patient was almost completely bedridden and considerably incapacitated, with bed-sores and an incontinent bladder. For the last year he was also having flexor spasms. There was no significant past illness. His mother was reported to have died of a similar illness in which she was completely bedridden, and all the other members of the family were known to have mottled teeth. His economic standard was very poor, and the diet was grossly deficient in essential nutrients.

Physical examination revealed a very poorly nourished and emaciated person. He had a generalized flexed and rigid decubitus, with a kyphosis of 30° and flexion deformity of the knees. The teeth showed grade 2 dental fluorosis (see pp. 360–1). Movements of the cervical and lumbo-dorsal spine, hips, and knees were markedly restricted. The maximum chest expansion was only one inch. Bony excrescences were palpable along the anterior surface of the tibia. Examination of the cardiovascular system, chest, and abdomen gave normal results. The blood-pressure was 120/70.

Nervous system. The higher cerebral functions, cranial nerves, and fundi were normal. There was appreciable wasting of both hands, especially in the thenar eminences. There was no wasting of the muscles in the lower extremities.

Muscle power, by the Medical Research Council (1954) standards, was grade 2 in the left hand and grade 3 in the other limbs. There was some degree of hypotonia in the upper limbs, and marked spasticity in the lower limbs. Sensations were lost up to the level of the third interspace; vibration sense was lost up to the iliac crests. The tendon reflexes of the lower extremities were markedly exaggerated. In the upper limbs the radial jerk was inverted on the left side, and normal on the right side. The abdominal reflexes were absent, and the plantar response was extensor on both sides. He had extensive bed-sores, and passed urine and stools in bed.

Investigations. The haemoglobin was 14·5 g. per 100 ml., red cells 4,900,000 per cu. mm., white cells 8,200, with 79 per cent. neutrophils, and erythrocyte sedimentation rate 25 mm. in one hour (Westergren). The urine on routine analysis and the stools were normal. Serological tests for syphilis were negative. The blood urea was 33 mg., calcium 9·4 mg., and phosphorus 3 mg. per 100 ml.; alkaline phosphatase was 8 King–Armstrong units. The cerebrospinal fluid was clear and colourless; the pressure was 80 mm. of water; proteins were 200 mg. per 100 ml., and globulins present; sugar was 48 mg. and chlorides 650 mg. per 100 ml., and cells normal. Myelography showed delay in the transit of the dye from the cisterna magna. Fluorine in the water consumed by the patient was 0·95 mg. per 100 ml. (9·5 p.p.m.), in the blood 0·61 mg. per 100 ml., in the urine 0·69 mg. per 100 ml., and in bone 630 mg. per 100 g. of ash. Radiography showed stage 3 fluorosis (see page 362) throughout the skeleton, with very advanced changes in the cervical spine (compare Plate 32, Figs. 1 to 3), pelvis, thoracic cage, skull, and bones of the extremities.

The patient was observed in hospital for about three months without any significant change. He died of urinary infection and secondary infection in the extensive bed-sores. A complete autopsy was performed, followed by maceration so as to preserve the skeleton as a whole. There were very extensive changes throughout the skeleton, most marked in the spine and pelvis. The whole spine showed an extreme degree of osteophytosis, particularly in the cervical region, where there was gross narrowing of the spinal canal. These skeletal changes are described in detail in a later section. The internal organs, including the heart, lungs, liver, spleen, and kidneys, were normal, and did not show any excessive fluoride deposition. The brain and its covering were normal. The spinal cord could not be obtained, since it was intended to macerate the axial skeleton in one piece.

Symptomatology

The onset was insidious in all cases, and the duration of the history of symptoms was very variable, usually extending to a number of years. Stiffness of the back and lower extremities was a universal complaint. The patients who had neurological manifestations complained of gradually increasing weakness of both lower limbs, which in 10 cases later extended to involve the upper limbs. In 11 cases weakness and spasticity were such that the patients were completely incapacitated and bedridden (Plate 33, Fig. 4). There was a history of paraesthesiae and numbness in 20 patients, flexor spasms in eight, impotence in five, radiating pains along the legs in seven, sphincteric disturbances in 18, and girdle sensations in six.

In considering the neurological manifestations of fluorosis it will be readily understood that the symptoms, as in cervical spondylosis, were those of a lesion

either of one or more nerve roots or spinal nerves, or of the spinal cord, or of both, so that any level or combination of levels of the spine were attacked. The radicular features were in the nature of acroparaesthesiae, pain referred along the myotome, or muscular wasting. The commonest symptom of involvement of the spinal cord was muscular weakness, which was usually confined to both

TABLE I

Symptoms of Endemic Fluorosis

	Number of cases	%
Stiffness or pain in the spine	60	100
Stiffness of other joints	39	65
Weakness of the lower limbs	25	41
Weakness of all four limbs	10	16
Weakness of only the upper limbs	2	3
Inability to walk	18	30
Completely bedridden state	11	18
Acroparaesthesiae	20	33
Flexor spasms	8	13
Impotence	5	8
Sphincter disturbances	18	30
Radicular pains in the upper limbs	5	8
Girdle sensation	6	10

lower limbs, sometimes in all four limbs, and very rarely in only the upper limbs. Besides these radicular and myelopathic symptoms, the other most characteristic complaint was a gradually increasing stiffness of the whole body, particularly of the joints, which caused peculiar complaints such as difficulty in squatting, difficulty in standing up from the sitting posture, inability to sit up in bed, and inability to lie prone. The chief symptoms observed are shown in Table I.

Physical Examination

The physical signs of fluorosis are predominantly found in the examination of the teeth, skeletal system, and nervous system.

Dental changes. Ever since the first description of mottled enamel by Black and McKay (1916), and the definite association of this anomaly with the fluorine content of drinking water by Churchill (1932), this peculiar form of dental dystrophy has attracted world-wide attention. Interest has been much enhanced by the public health programmes of fluoridation in order to prevent dental caries. It has been definitely established that mottling of the enamel occurs only if the fluorine content of water is above 2 to 3 p.p.m., or certainly above 1 p.p.m. (Smith, Lantz, and Smith, 1935). With these or higher concentrations of fluorine in water, and certain other factors which are not yet completely understood, the dental changes are divided into three stages:

Grade 1. The enamel loses its normal translucency, either in spots or diffusely, and becomes turbid or white like chalk.

Grade 2. A dark pigment is deposited in the defective enamel. The colour may vary in intensity from yellow or brown to black. The nature of the pigment deposited in the defective enamel is still unknown.

Grade 3. In addition to the above changes, there is a definite pitting all over the teeth.

Mottling of the enamel occurs only if the child lives in the endemic area during the period of calcification of the teeth, namely from birth to the age of 12 to 14 years, and such teeth are remarkably resistant to caries. Dental fluorosis of grade 1 was present in six, grade 2 in 20, and grade 3 in 22 cases of the present series. It is significant, however, that 12 patients (20 per cent.) had no mottling of the teeth. In a field survey in the endemic area 786 school children were examined, of whom 67 per cent. showed changes typical of dental fluorosis, 40 per cent. being in grade 1, 25 per cent. in grade 2, and 2 per cent. in grade 3. The radiological appearances in the teeth are illustrated in Plate 33, Fig. 5.

Skeletal changes. The changes in the skeletal system are among the most interesting and distinctive features of chronic fluorine intoxication, and are responsible for most of the complications. They will be described under the following headings: (1) gross changes found by clinical and macroscopic examination; (2) radiological features; (3) deformities; (4) histopathological studies; (5) chemical composition.

1. *The gross changes* in the skeleton are well illustrated in the case studied at autopsy by Singh, Dass, Hayreh, and Jolly (1961). Almost all the bones were affected by such a degree of intoxication, though the brunt of the disease fell on the axial skeleton. The bones were dull in colour and markedly irregular in their contours, and were abnormally heavy owing to excessive deposition of fluorides. The sites of muscular and tendinous insertions were rendered abnormally prominent by excessive periosteal reaction with development of multiple exostoses. The calcification was observed along the attachment of muscles and tendons and, in the extremities, in the interosseous membranes and around the joint capsules. The irregular deposition of fluorides often gave the bones grotesque physical features (Plate 34, Fig. 6). The greatest changes were observed in the spine, particularly in the cervical region. The vertebrae showed altered proportions and measurements in all planes, but the striking abnormality was the gross reduction of the anteroposterior diameter of the spinal canal, which in one case was reduced to 3 mm. at the level of the third and fourth cervical vertebrae. When it is realized that the average anteroposterior diameter of the spinal cord in the cervical enlargement is 8 mm., and the bulge of the ligamentum flavum has also to be accounted for, it is evident that with this degree of narrowing compression of the cord is inevitable. Moreover, there were irregular exostoses along all the surfaces, with calcification of intervertebral disks and cartilaginous ligaments. The vertebrae were fused at many places, so that the spinal column was made rigid. Similarly, the intervertebral foramina were much reduced, a change which explained the radicular features observed in many cases. There were not many gross changes in the skull, except

that irregular bone projected from the margins of the foramen magnum, reducing its size. Other foramina in the skull were not affected. In 10 cases the irregular deposition of bone was clinically obvious as bony excrescences, varying in size from 2 mm. to 2 cm. They were frequently observed near the knee joints, along the anterior surface of the tibia. The skeletal changes caused gross limitation of movements, particularly of the cervical spine, lumbo-dorsal spine, hip joints, and knee joints, in that order of frequency.

2. *The radiological appearances* are characteristic and diagnostic (Møller and Gudjonsson, 1932). Sclerosis of bones was observed throughout the skeleton, with calcification of ligaments and muscular attachments. Roholm (1937) divided the degree of skeletal affection into three stages. In the first stage the spinal column and pelvis show roughening and blurring of the bone trabeculae. In the second stage the bone structure is blurred and the bone contours become uneven. In the third stage the bones show the appearance of marble, with a woolly configuration. The bones of the extremities show irregular periosteal thickening and calcification of ligaments and muscular attachments. The radiological findings observed by us are summarized as follows:

	Stage 1	*Stage 2*	*Stage 3*	*Total*
Neurological cases . . .	—	12	15	27
Non-neurological cases . .	8	10	15	33
				60

The most pronounced changes were seen in the vertebral column, particularly in the cervical region. Osteosclerosis and irregular osteophyte formation were noticed in the vertebral body, the transverse and spinous processes, and the pedicles and laminae. Beak-like lipping and a chalky-white ground-glass appearance of the entire vertebral column were the characteristic radiological features, along with calcification of the intervertebral ligaments. As a result of the irregular exostosis there was considerable encroachment on the diameters of the intervertebral foramina and the spinal canal. Next to the spine, osteosclerosis was most evident in the pelvis, with a characteristic calcification of the sacrospinous and sacrotuberous ligaments. The capsule of the hip joint was very often calcified with irregular lipping from the acetabulum. The cortical portion of the long bones was dense and thick, with reduction of the marrow cavity. Irregular periosteal bone formation was observed along the tendons and the fascial and muscular attachments, for example, on the interosseous membrane of the forearms and legs (Plate 34, Fig. 7), the linea aspera, the deltoid tuberosity, the lower margins of the ribs, the attachments of the tendo Achillis, the tibial tubercle, and the greater trochanter of the femur. Skiagrams of the chest revealed a peculiar contrast of the marble-white bony cage with the radiotranslucent lungs, which appeared emphysematous. The skull changes were not very striking, although thickening of the vault of the skull was obvious, with sclerosis near the suture lines. The sella turcica and the nasal sinuses were normal in most cases. There was no significant narrowing of the foramina at the base of the brain.

A comparison of the radiological features of the neurological and non-neurological cases revealed that involvement of the skeleton was more widespread and severe in degree in the former, indicating that such examples were probably due to a severe fluorotoxicosis. It is interesting that calcification of the laryngeal cartilages was observed by us in four cases, and was confirmed in the case studied at autopsy. The degree of osteosclerosis was found to be related to the duration of intoxication and to the concentration of fluorine in water. Physical strain was also a possible factor; the greater the strain, the more pronounced were the skeletal changes.

TABLE II

Incidence of Deformities

	Neurological cases	*Non-neurological cases*	%
Kyphosis	8	4	20
Flexion deformity of knees .	6	0	10
Flexion deformity of hips .	6	0	10
Generalized flexion . .	8	10	30
Fixation of thoracic cage .	15	15	50

3. *Deformities* (Table II). Skeletal intoxication lasting for a number of years ultimately led to crippling deformities, due partly to mechanical factors and partly to immobilization necessitated by pain and paraplegia. Such deformities were encountered in 25 cases, the most common being kyphosis, flexion deformity of the hips, flexion deformity of the knees, and fixation of the chest in the position of inspiration due to calcification of the costal cartilages.

4. *Histopathological data* in endemic fluorosis are very scanty, and studies have been chiefly limited to observations in experimental animals. In the present series the histopathology of the bones was studied in seven cases, in six by open bone biopsy obtained from the tibia or iliac crest, or both, and in one from autopsy. In general, the long bones showed two zones of bony tissue, the compacta and a thin irregular peripheral tissue resembling spongy bone. The compacta showed the characteristic histopathological picture of skeletal fluorosis, with disordered lamellar orientation and an enlarged poorly formed Haversian system, resembling very much the histopathological changes observed in experimental animals (Weatherell, 1960) (Plate 35, Figs. 8 and 9). In the spongy bone (iliac crest and vertebral bodies) pieces of osteoid tissue were found among well-formed bone trabeculae. Some of the irregular pieces of osteoid tissue extended on to the attached muscle. The bony trabeculae were very dense in places and contained a considerable amount of calcium. The areas around the vascular spaces stained deeply with eosin. In two other cases the only tissue procured by the biopsy needle was the calcified muscular attachment. It showed skeletal muscle infiltrated with areas of irregular calcification. Several

trabeculae of osteoid tissue and an occasional bony trabecula were also seen. Crystals of fluoride material, as described by Roholm (1937), could not be demonstrated in our sections.

5. *Chemical composition.* The exact pathogenic mechanism by which fluorine exerts its deleterious effects is not known. It is probable that initially there are changes in the chemical composition and deposition of bone salts in the structure and constitution of organic matrix, probably mediated by altered enzymic reactions. Roholm (1937) believed that fluorides were probably deposited in the form of calcium fluoride along with the calcium phosphate of the bones, but the work of Weidmann, Weatherell, and Whitehead (1959) demonstrated a decrease of carbonate and an increase of magnesium in the exostotic bone, which suggests a replacement of the CO_3 or HCO_3 groups in bone salts and a precipitation of MgF_2 upon or within the bone matrix. It appears unlikely, however, that the changes in the chemical composition of bone salts account for the pathological changes found in fluorosis. In the present investigation chemical studies were limited to the determination of fluoride in mg. per 100 g. of bone ash, the normal figures being 110 ± 20 mg. (Zipkin, Lee, and Leone, 1958). Such studies, undertaken in 10 cases, yielded results above normal, varying from 70 to 680 mg. per 100 g. of bone ash.

Neurological Manifestations (Fluorotic Radiculo-Myelopathy)

Involvement of the nervous system in skeletal fluorosis has been reported exclusively from India. Our interest in this problem was aroused by the fact that, while investigating obscure cases of paraplegia in Panjab, we were struck by the osteosclerosis and osteophytosis of all the vertebrae shown on radiography. Subsequently it was noticed that nearly all such cases were coming from a limited geographical area. This clue prompted an extensive epidemiological and clinical investigation in the Bhatinda district of this province (Singh, Jolly, and Bansal, 1961). The credit for the earliest description of neurological cases again must be given to Shortt, Pandit, and Raghavachari (1937), who described 10 such cases from the Nellore district of Madras. A few sporadic cases have since been described from different parts of India, but the only authentic study is that of Siddiqui (1955). As shown in Table III, 45 neurological cases have so far been described, but none of the earlier authors have attempted to define the exact pattern of the neurological manifestations. Despite the alarming radiological appearances of advanced fluorosis, the changes in the spine are themselves symptomless, or at the most cause some discomfort, occasionally amounting to actual pain, especially on extremes of movement. It is only when the nervous system is involved that attention is directed to the gravity of the disease, which soon leads to extreme crippling and gross invalidism.

The duration of the history of neurological manifestations was extremely variable, ranging from a few months to 10 years. In the majority of cases it was more than one year; the average duration was 2·2 years. The symptoms

of spinal cord lesions tended in general to develop slowly, and then to progress insidiously over the first one or two years, after which they remained almost stationary. In two cases the onset was sudden, and was obviously related to trauma sustained by the patients, which in the ordinary course of events was not sufficient to produce neurological deficit. Symptoms may be due to a lesion of one or more nerve roots, or to involvement of the spinal cord. It will be convenient to consider the radicular and myelopathic symptoms separately, although it was not always possible to make a sharp distinction.

TABLE III

Neurological Cases of Fluorosis

Authors	*Total cases of fluoro-toxicosis*	*Neuro-logical cases*
Shortt, Pandit, and Raghavachari (1937)	10	10
Khan and Wig (1945)	2	—
Lyth (1946)	1	1
Satyanarayana Murthi, Rao, and Venkateswarlu (1953)	1	1
Siddiqui (1955)	32	32
Janardhanan and Venkaswamy (1957) .	1	1
Kasliwal and Soloman (1959)	1	—
Present series	60	27
	108	72

Radicular features. The most important were those of (1) muscular wasting; (2) acroparaesthesiae; and (3) subjective pain referred along the nerve roots. Subjective complaints such as acroparaesthesiae and pain were almost universally present, although these complaints were not voluntarily offered until the subjects were questioned about them. The most important radicular feature was the weakness and wasting of muscles. This was usually asymmetrical, involving most often the small muscles of one or both hands. The mechanism of muscular wasting is probably similar to that found in cervical spondylosis, as pointed out by Frykholm (1951), and due to selective damage to the anterior spinal roots from compression by the lower part of the foramina. In some cases the muscular wasting may be due to atrophy from disuse. In a few patients, besides the muscular weakness, there was fibrillation, so that the condition was very often mistaken for motor-neurone disease. In five cases there were chronic multiradicular symptoms.

Myelopathic features. The earliest symptom of involvement of the spinal cord was weakness of both lower limbs, usually starting in one leg, the other becoming involved after some time. This weakness was observed in all cases. In 10 cases, after a variable interval, the upper limbs were also involved, producing a spastic quadriplegia. Paraesthesiae in a limb or limbs were frequent. The symptoms and signs of myelopathy resembled in many ways those of spondylitic myelopathy, and the latter are so well known that it is proposed to refer only to some of the salient features in relation to the pathological anatomy.

In general, the symptoms progress fairly quickly, and the common tendency is towards progressive deterioration and restriction of activity. The physical signs of fluorotic myelopathy depend chiefly upon the anatomical factors of maximum narrowing of the spinal canal or of the intervertebral foramina, and whether the compression is chiefly at a single site or multiple. Muscular wasting was not a very prominent sympton in the present series, being present in seven cases. It was usually confined to the hand muscles or muscles of the forearm, and most conspicuous in the hands. Fasciculation was observed in only two cases. The site of muscular wasting is not always closely correlated with the site of compression, for, although wasting of the hands is likely to be severe when the last cervical and first dorsal segments of the cord are compressed, it may be almost equally severe when the protrusion is at a higher level, and even as high as C3–4, probably as a result of interference with the blood-supply to the lower segments of the cervical enlargement. The tone of the muscles in the extremities was almost universally increased. This was predominantly due to an upper motor neurone lesion, although the muscular and skeletal changes of fluorosis contributed partly to the spasticity observed in most of the patients. In four very advanced cases the spasticity was extreme, so that it was impossible to bend one limb individually, and the whole of the skeleton moved as one unit. This was partly explained by the development of contractures around the knees and hips. The upper limbs were involved in 10 cases, while the disease was mainly confined to the lower limbs in 17.

Eighteen of the 27 neurological patients had some kind of sensory disturbance, though the sensory changes were inclined to be patchy. In nine cases sensory loss resembled that due to compression by a tumour, all modalities of sensation being affected below a sharp level, usually around the umbilicus. Light touch was much less involved than other sensations. Posterior-column sensations were more severely affected than the spinothalamic, although the latter were not always spared. In the upper extremities paraesthesiae and sensory disturbances were confined to a single dermatome distribution in four cases, and in another four they had a 'glove' distribution, involving all the digits of both hands, with acroparaesthesiae. It seems that in such cases the sensory disturbance in the upper limbs was due to the involvement of sensory tracts in the cord rather than of the posterior roots.

The tendon reflexes were almost invariably exaggerated in the lower extremities, though in advanced cases contractures of the knees made it very difficult to elicit the reflexes. The deep reflexes in the upper limbs were exaggerated in seven cases and absent in three, depending upon the level of the cervical lesion and the combination of upper and lower motor neurone lesions. An inverted supinator jerk was present in five out of the 10 cases in which there was a neurological deficit in the spinal cord at the fifth cervical segment. The abdominal and plantar reflexes showed the usual signs of a bilateral pyramidal lesion, the latter being extensor in 22 patients, equivocal in three, and flexor in two. Disturbances of function of the sphincters were seen in the form of hesitancy or incontinence of micturition in 18 cases. In advanced cases the

features of paraplegia in flexion gradually ensued, with flexor spasms. The active and passive movements of the spine, as of all other joints, were much restricted and painful, and a kyphotic deformity was seen in 10 patients.

In two cases the neurological deficit was obviously related to trauma of the cervical cord, although the violence was not sufficient in the ordinary course of events to produce this injury. Certain other neurological features, such as auditory nerve disturbance (Siddiqui, 1955), tetaniform convulsions (Waldbott, 1957), cephalalgia (Waldbott, 1960), and electroencephalographic disturbances, have been described, but were not observed by us. It was extremely difficult to

TABLE IV

Fluoride Estimation

	Normal (*Roholm, 1937*)	*Present series*	
		Range	*Average*
Blood (mg./100 ml.)	Traces	0·05–0·61	0·15 (1·5 p.p.m.)
Urine (mg./100 ml.)	Less than 0·18	0·17–2·5	0·76 (7·6 p.p.m.)
Bone (mg./100 g. of ash)	110±20	70–680	343
Water (mg./100 ml.)	Less than 0·1	0·12–1·4	0·59 (5·9 p.p.m.)
Soil (mg./100 g. of dried matter)	Less than 2	6·7–8·5	7·3

enter the subarachnoid space by either the lumbar or the cisternal route, owing to the extreme degree of calcification of the intervertebral disks and ligaments. Consequently the composition and dynamics of the cerebrospinal fluid could be studied in only 10 cases. In three the proteins were increased to more than 200 mg. per 100 ml. The pressure of the cerebrospinal fluid was very low, indicating a partial block in the subarachnoid space. For similar reasons myelography was possible in only four cases. In one patient the dye remained in the cisterna magna for three or four days; in the second there was a considerable delay in transit of the dye in the cervical region; in the third and fourth patients there was a complete block at D8 and C3 respectively (Plate 35, Fig. 10).

Thus the clinical picture of fluorotic myelopathy may closely simulate cervical spondylosis, extramedullary and intramedullary tumours of the spinal cord, subacute combined degeneration of the cord, syringomyelia, and motor neurone disease. Besides the differences in the clinical description, the skeletal and radiological changes associated with the neurological lesions make fluorosis sufficiently distinctive.

Laboratory Data

There were no significant abnormalities in the blood, urine, and stools. Two patients had a moderate microcytic hypochromic anaemia. The erythrocyte sedimentation rate varied from 2 to 67 mm. in one hour (Westergren), the average being 21 mm. The study of kidney function by estimations of blood urea and urea clearance did not reveal any significant abnormality. This finding is in striking contrast to industrial and experimental fluorosis, in which kidney damage is the earliest change (Lindemann, Pindborg, and Poulsen, 1959).

Serum calcium was estimated in 25 cases. It ranged from 9 to 13·5 mg. (average 10·2 mg.) per 100 ml. Serum inorganic phosphorus ranged from 1·9 to 6·1 mg. (average 3·45 mg.) per 100 ml. Alkaline phosphatase ranged from 4 to 46 King–Armstrong units, the average being 12·2 units. Similarly, the total 24-hour urinary excretion of calcium estimated in 12 cases was within normal limits. Estimations of total and differential blood proteins, and other liver function tests, were made in 11 cases, and were within normal limits.

Fluoride estimation was done by thorium nitrate titration, and significantly high levels were found in nearly all the biological fluids (Table IV).

Discussion

Public health programmes to prevent dental caries by artificial fluoridation of drinking water have always considered the possibility of cumulative toxic effects. Studies of this nature have been attempted particularly in America (Geever, Leone, Geiser, and Leiberman, 1958), and it has been stated that fluoride ion even in as high concentration as 12 p.p.m. is comparatively innocuous. On the other hand, in India, increasing numbers of cases of endemic fluorosis have been reported which clearly bring out the toxic potentialities of this ion, especially in high concentrations. The toxicity of fluorine has been tabulated as follows by Hodge (1960):

2 p.p.m. (air)	Injury of certain plants.
1 ,, (water)	Reduction of dental caries.
2 ,, (water)	Mottled enamel (first eight years of life).
8 ,, (water)	10% incidence of osteosclerosis.
20 to 80 mg. per day (ingested)	Crippling fluorosis (10 to 20 years of age).
More than 50 p.p.m. (water)	Thyroid changes (structure and function).
100 p.p.m. (water)	Growth retardation.
More than 125 p.p.m. (water)	Kidney changes.
2·5 to 5 g. (ingested)	Lethal single dose.

The importance of this subject from the social and preventive aspects in India and elsewhere is obvious.

Although endemic fluorosis has been described for many years, its neurological complications have received scant attention. They are due to a slow and gradual compression of the spinal cord and nerve roots, and in general the clinical picture is remarkably similar to that of cervical spondylosis (Brain, 1954, 1955; Logue, 1957). This is easily understandable because, although cervical spondylosis is a degenerative condition and fluorosis a form of chronic intoxication, the pathogenesis of neurological involvement and the end-results in both conditions are similar. There is, however, one important difference, in that the neurological complications of fluorosis are predominantly in the nature of a

myelopathy, while in cervical spondylosis the radicular features are a more essential part of the clinical findings. The pathogenesis of fluorotic myelopathy is complex. In all probability the cause of spinal cord malfunction resembles the effect of a tumour, the cord being displaced backwards and compressed against the laminae and ligamentum flavum by the projecting exostosis, which is large enough to cause obstruction, as shown by manometry and myelography, with a considerable increase of proteins in the cerebrospinal fluid. Involvement of the spinal cord, however, can be due to a number of different mechanisms, as is already known in the case of cervical spondylosis.

1. When the osteophyte is large enough, the cord may be directly compressed between it and the lamina posteriorly. The average anteroposterior diameter of the spinal canal in the region of the lumbar vertebrae is 14 to 15 mm., and in the cervical region 10 to 12 mm. With a large osteophyte this diameter may be reduced to 8 or 10 mm. in the lumbar and to 4 or 5 mm. in the cervical region. The average anteroposterior diameter of the spinal cord in the cervical enlargement is 8 to 9 mm., and it is evident that with this degree of narrowing compression of the cord is almost inevitable.

2. The compression may operate indirectly by interfering with the blood-supply of the spinal cord, an effect which has been investigated in detail by Mair and Druckman (1953). The compression and distortion of the cord by an anterior protrusion may interfere with the blood-flow either in the main trunk of the anterior spinal artery or in its branches, or both. This mechanism may be responsible for symptoms developing above the level of the disk protrusion. The blood-supply to the spinal cord may be further impaired by narrowing of the intervertebral foramina through which the radicular arteries penetrate.

3. Another attractive hypothesis pertains to the role of the dentate ligaments, as suggested by Kahn (1947) in relation to cervical spondylosis. If the cord is tethered by dentate ligaments, the mechanical result of backward displacement produced by the protrusion would be an area of primary stress in the anterior columns, and an area of secondary stress in the vicinity of the attachment of the ligaments and the meridian of the cord, subjacent to which lie the pyramidal tracts. Both areas would be under equal stress, but, owing to the larger fibre-diameter of the pyramidal tracts and their higher oxygen consumption, they could suffer more severely. The posterior columns, being free of pressure, may relatively escape. This result is in conformity with the clinical description of the disease.

4. Because of the synostosis of the intervertebral joints and calcification of the intervertebral disks, there is great limitation of the normal movements between two adjacent vertebrae, with abnormal stresses at certain regions of the spinal column. Symonds (1953) has drawn attention to the increased vulnerability of the fused cervical spine to injury by over-extension, and has quoted several instances in which myelopathy developed as a result of trivial trauma. A similar mechanism was possibly responsible in two patients of the present

series, in whom a minor injury produced a sudden quadriplegia. Moreover, fluorotic bones are more brittle than normal (Roholm, 1937), and this factor may be the basis of a neurological lesion in some cases.

5. The complex series of changes known as 'root sleeve fibres', affecting the investment of nerve roots and radicular nerves through chronic irritation and compression, is certainly possible in fluorotic radiculopathy; for calcification of the intervertebral disk initiates a series of changes comparable to that seen in cervical spondylosis.

The degree of disability and the time of onset of symptoms in skeletal fluorosis are probably related to the concentration of fluorine in water, and the patients with fluorotic radiculomyelopathy probably represent the more advanced and severe examples of skeletal fluorosis. A number of other factors have been described which may determine the severity and the complications of fluorosis. Two of these, the meteorological factor and the nutritional status, certainly play a part so far as the intoxication in India is concerned (Pandit, Raghavachari, Rao, and Krishnamurti, 1940; Daver, 1945). The hot weather markedly increases the amount of fluoride which is ingested in water, and also raises its concentration. The protective action of calcium against the toxic action of fluorine has been demonstrated in monkeys by Pandit and Narayana Rao (1940). Pandit, Raghavachari, Rao, and Krishnamurti (1940) found that vitamin C lessened the severity of fluorosis in experimental animals. It seems certain that lower temperature and better nutritional status are some of the factors which afford protection against a crippling fluorosis and the development of neurological manifestations in countries such as the United States, where areas of equally high fluoride content in water and soil have been described.

We are extremely grateful to Dr. P. Devi, of the Central Research Institute, Kasauli, for some of the fluorine estimations, and to Dr. M. Balasubrahmanyan and Dr. S. D. Khanna for the histopathological studies. Our thanks are also due to Dr. J. A. Weatherell and Dr. G. L. Waldbott, of Detroit, Michigan, for some useful suggestions. The field survey was carried out by Dr. S. Singh and Dr. B. C. Bansal. We are also indebted to Dr. Ramji Dass and Dr. Sohan Singh for the study of a fluorotic skeleton, to Dr. Ram Dass and Dr. Vazirani for the radiological work, and to Mr. G. S. Sekhon for the photographs.

Summary

Endemic fluorosis is a form of chronic fluorine intoxication due to ingestion of large quantities of fluoride-rich water spread over a number of years. It produces a well-defined systemic disorder in which the teeth, skeletal system, and nervous system are involved in that order.

The teeth show the characteristic mottling in a high percentage of cases. The bones are rendered osteosclerotic, and show characteristic radiological features due to the deposition of fluoride salts. The axial skeleton, and particularly

the cervical spine, show the greatest changes, resulting in considerable narrowing of the spinal canal.

The pattern of neurological disorder associated with advanced cases is described. It is designated as fluorotic radiculo-myelopathy, and often resembles cervical spondylosis.

Sixty cases of skeletal fluorosis are described. Twenty-seven showed the neurological complications of fluorotic radiculo-myelopathy. The pathogenesis of the neurological complications is briefly reviewed.

Significantly high levels of fluorine are described in the blood, urine, and bones of these patients, and in the water and soil samples of the area in which they resided. A characteristic histopathological picture of skeletal fluorosis is described.

The importance of this work from the social and preventive aspects is obvious.

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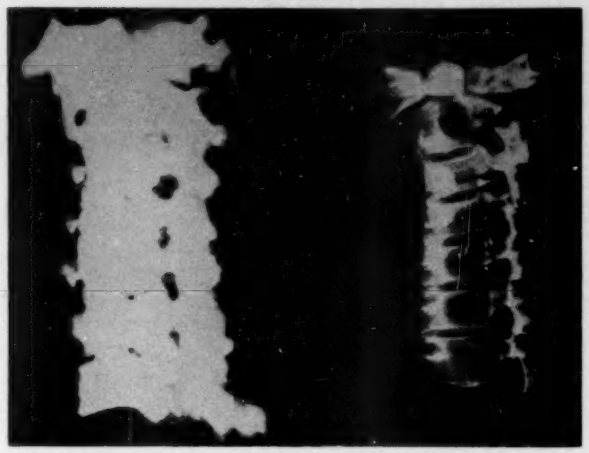


FIG. 1. Post-mortem radiograph of the cervical spine from a case of fluorosis compared with a normal cervical spine. Note the marked osteosclerosis and osteophytosis, with narrowing of the intervertebral foramina

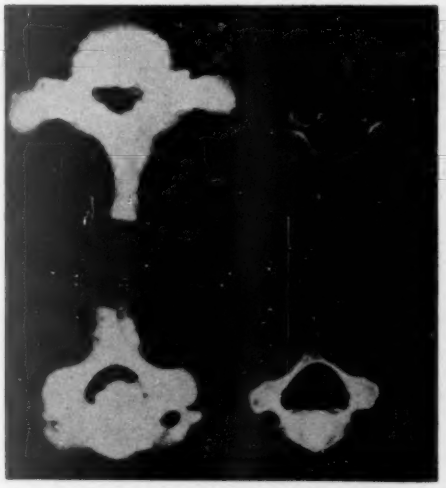


FIG. 2. Skiagram of the cervical and dorsal vertebrae from a case of fluorosis compared with normal vertebrae. The anteroposterior diameter of the spinal canal is markedly reduced

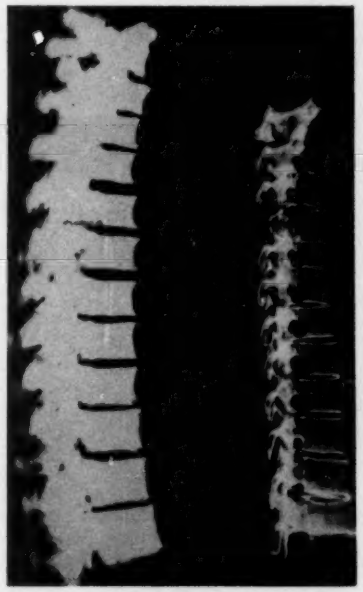


FIG. 3. Radiograph of the spine from a case of fluorosis compared with normal

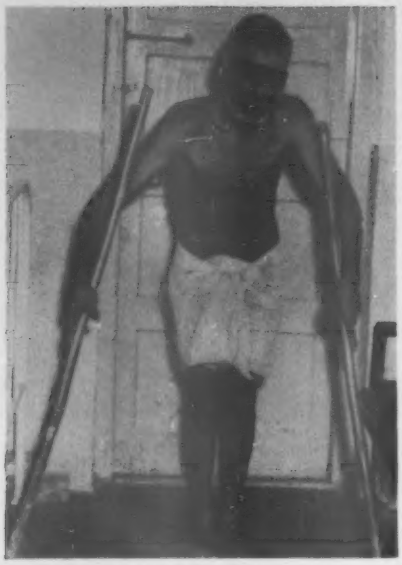


FIG. 4. A patient with advanced fluorosis and paraplegia

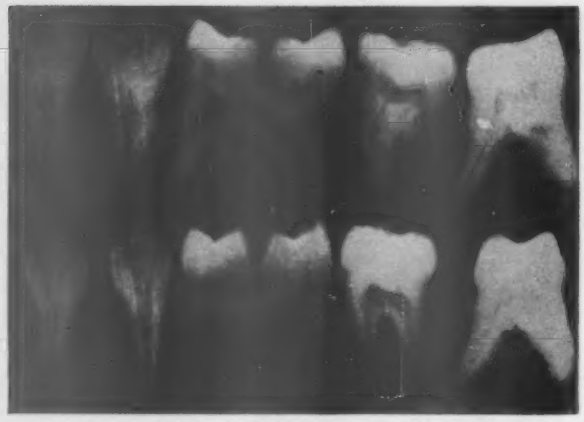


FIG. 5. Skiagrams of the teeth from a case of fluorosis compared with normal. Note the increased bone formation near the roots of the teeth. Mottling of the enamel is seen clinically on the exposed portion of tooth

FIG. 6. Skeleton from a case of fluorosis showing irregular bone deposition

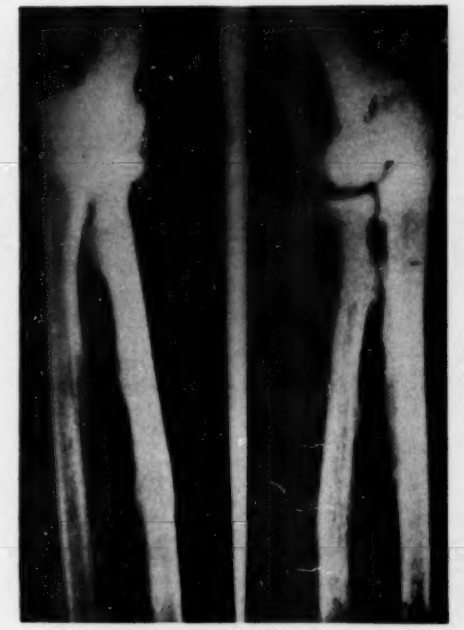
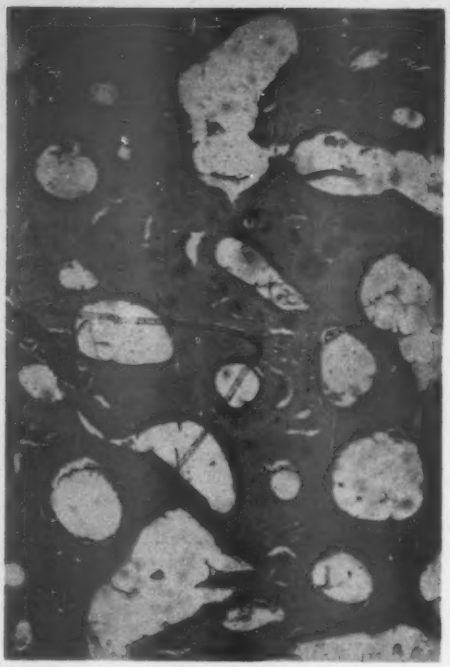


FIG. 7. Radiograph of long bones showing calcification of the interosseous membrane



FIGS. 8 and 9. Histopathological section showing disturbances of the Haversian system and disordered lamellar orientation

FIG. 10. Myelogram showing obstruction of the dye in the cervical region

616.15:547.979.733(68)

PORPHYRIA IN THE AFRICAN[1]

A Study of 100 Cases

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With Plates 36 to 39

It has only recently been recognized that porphyria is a condition which is not uncommon in Africans (Barnes, 1959). The nature of porphyria in this group seems unusual in that evidence of genetic origin is exceptional, in contrast to the malady in white South Africans, in whom a genetic origin is the rule in most cases. Furthermore, the pattern of porphyrin excretion differs fundamentally (Barnes, 1959; Eales, 1960); and, finally, there appears to be a remarkably uniform clinical pattern in most African patients. It is uncertain whether the disease in Africans is of recent occurrence, perhaps related to the profound changes which have taken place in their mode of living over the past 50 years, or whether the condition has passed unrecognized during this period. Our experience in King Edward VIII Hospital is that undoubtedly numbers of cases have passed unnoticed, or have in previous years been wrongly diagnosed as pellagra (a condition, however, which we have occasionally found occurring concomitantly with porphyria).

Specialized hospital services have become available to the African only during the past two decades, and such services are at present very inadequate to meet the heavy demands placed upon them by a largely sub-economic community. In addition, porphyria as it affects the African is essentially a benign condition, usually causing very slight disability, so that it is often difficult to persuade the patient, especially a wage earner, to enter hospital. Any investigation into porphyria in the African population must therefore be planned to include patients studied at the out-patient level; Africans are difficult to control as out-patients, being somewhat elusive in their movements. Finally, the out-patient departments in most African hospitals are grossly overcrowded and under stress; the turnover of patients at King Edward VIII Hospital, for example, is nearly 600,000 per annum. These factors may explain the paucity of full-scale studies of porphyria in African subjects.

Patients Investigated

The first 15 cases were selected primarily for liver biopsy, and consisted of 13 male and two female patients (Lamont and Hathorn, 1959). The remaining

[1] Received January 23, 1961.

85 patients represent consecutive cases encountered by one of us (N.M.L.) over a period of 12 months, and constituted the majority of cases of porphyria attending the out-patient department of King Edward VIII hospital during this period. Sixty-two of the 100 patients were admitted to hospital, the remainder being examined as out-patients. In the majority of the 100 patients it was possible to undertake serial examinations. All clinical examinations were performed, and data recorded, by one of the authors (N.M.L.), who took histories in the language of the patient (usually Zulu). The data were recorded on

TABLE I

Age and Sex Distribution

	Age, in years						
Sex	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*71–80*	*Total*
Male patients	9	22	17	8	3	0	59
Female patients	7	15	12	4	2	1	41
Total	16	37	29	12	5	1	100

standard forms. Routine chest X-rays were done in 79 cases. Specimens of urine, faeces, and blood were collected in the wards or in the out-patient department. Liver biopsies were performed on 28 of the 100 patients. In addition, autopsy material was available from two patients who died of other diseases. The age and sex distribution of the 100 patients is shown in Table I.

Methods

Porphyrin in stools and urine. In 35 patients the presence of porphyrin in the urine was demonstrated by Wood's light and spectroscopic examination. In the remaining 65 patients quantitative estimations in urine and faeces were performed by the following methods.

Urine. Total porphyrins were estimated by the method of Sveinsson, Rimington, and Barnes (1949), and δ-aminolaevulic acid and porphobilinogen by the method of Mauzerall and Granick (1956). These examinations were commenced within an hour of collection. Coproporphyrin was estimated by the method of Holti, Rimington, Tate, and Thomas (1958).

Faeces. A screen test was carried out, using an acetic acid-ether extract of a fragment of stool and examination of the extract under Wood's light; if positive, coproporphyrin and protoporphyrin were determined by the method of Holti, Rimington, Tate, and Thomas (1958).

Serum glutamic-oxalacetic acid transaminase (G-OT) was recorded in Karmen units per ml., using the method described by Karmen, Wróblewski, and LaDue (1955). The room in which transaminase examinations were carried out is air-conditioned, and temperature variation seldom exceeds 3° C; the results are therefore uncorrected for temperature.

Serum electrophoresis was performed by the method of Joubert, Hookins, and Hunter (1959).

Plasma iron and total iron-binding capacity were estimated by the methods described by Peters, Giovanniello, Apt, and Ross (1956).

Other investigations included blood counts, measurements of serum bilirubin and alkaline phosphatase (King–Armstrong units), prothrombin indices, and Wassermann reactions, and were carried out in the majority of patients.

Liver biopsy was undertaken via the transabdominal route. All specimens were embedded in wax, and stained with haematoxylin and eosin, for iron (Dry, 1945), by the Masson method for connective tissue, and for reticulin. Five specimens were examined macroscopically within 30 minutes of biopsy under Wood's light.

TABLE II

Symptomatology on Direct Questioning

Symptom	*Number of cases*
Active skin lesions (vesicles, ulcers, skin fragility)	82
Increased pigmentation of face	100
Urine 'red'	98

Clinical Features

A. *History*

We have examined the symptomatology in some detail, because it has been our experience that porphyria in the African may easily pass unnoticed by both the patient and the doctor.

Symptoms referable to porphyria are shown in Table II. It is of interest to note that every patient had noticed an increased darkening of the face, and nearly all either had active skin lesions or bore the scars of previous vesicles. All but two patients had noticed the passage of red urine.

Presenting symptoms. In contrast to the above findings, only 59 patients presented themselves at hospital because of porphyric cutaneous lesions. Subsequent investigation showed a number of these patients to be suffering from other diseases as well, for example tuberculosis. In addition to these 59 patients, five complained of a progressive darkening of their faces of recent onset—a symptom which we now consider essential to porphyria in the African. Three had no complaints at all, being found in the out-patient department accompanying other patients. The remaining 33 patients presented symptoms referable to other diseases, namely:

(*a*) Gastrointestinal disease (eight patients) (see below).

(*b*) Nervous disease (five patients): epilepsy (two); peripheral neuritis (two); psychosis (one).

(*c*) Pellagra (six patients). A seventh patient with pellagra complained mainly of porphyric skin lesions.

(*d*) Respiratory disease (four patients): pneumonia (three); pulmonary tuberculosis (one).

(e) Other disorders (10 patients): cardiac failure (two); leprosy (two); backache (four); loss of weight (one); hypoglycaemic coma (one).

Thus it is evident that in our African patients the symptoms of porphyria may pass unnoticed unless specifically sought; and such symptoms are often benign and incidental to other diseases.

TABLE III

Dietary Grading in 96 Cases of Porphyria compared with 239 Consecutive Ward Cases

Dietary grading	*96 porphyria cases*	*239 consecutive ward cases*
I	34 (35·4%)	54%
II	58 (60·4%)	37%
III	4 (4·2%)	9%

TABLE IV

Alcoholic Habits in 96 Cases of Porphyria compared with 239 Consecutive Ward Cases

Alcohol consumed	*By 96 porphyria patients*	*By 239 consecutive ward patients*
Nil	2 (2%)	20%
'Kaffir beer' only . .	23 (24%)	58%
'Kaffir beer' plus 'shimiyane' and/or 'gaveen' . .	71 (74%)	21%

Duration of the longest symptom attributable to porphyria. The shortest history recorded was two weeks, and the longest 13 years. Twenty-six patients gave a history of six months or less, 54 one of seven months to two years, and the remaining 20 a history longer than two years. Eighty per cent. of all the patients gave a history of two years or less.

Other symptoms. Of the 33 patients who had *abdominal pain*, eight were suffering from a variety of disorders which included primary carcinoma of the liver (two), amoebic liver abscess (one), cirrhosis (two), and dysentery (three). Of the remaining 25 patients all except two had only vague abdominal discomfort, which was certainly not suggestive of that found in acute intermittent porphyria, or of the South African variegate type described by Dean and Barnes (1959). One of the other two patients had concomitant stool-positive amoebic dysentery on admission, and developed ileus after specific antiamoebic therapy had been instituted. It was thought at the time that the treatment (emetine, diodoquine, and chloroquine) might have been a factor in precipitating ileus in a patient suffering from florid cutaneous manifestations of porphyria. The second patient, also with marked cutaneous lesions, developed transient ileus for no obvious reason. Symptoms related to the *nervous system* were found in 73 patients, but objective evidence of neurological disorder was present only in 58 (see below).

Personal habits. The patients' diets were graded in 96 of the 100 cases, the method of grading being that previously adopted in similar surveys (Lamont,

1960): *grade I*: maize the staple food, constituting more than 70 per cent. of the caloric value; with supplements of wheat, vegetable, dairy, and meat products once a week or less often; *grade II*: maize still the staple food, but with the above supplements taken more frequently than once a week; *grade III*: a diet approaching European standards, in which maize was not the staple food. Table III shows the dietary range in 96 of our cases compared with that found in a consecutive series of 239 male patients interrogated in a medical ward (Lamont, 1960). Our porphyria patients appeared to consume a somewhat better diet than the average patient found in the medical wards of this hospital.

Alcohol consumption. Except in a few exempted persons, the consumption of alcohol apart from 'kaffir beer' (a brew made from corn either domestically or by various local authorities) is illegal for the African. There are, however, a number of illegal concoctions freely available to him, the two main ones being 'shimiyane', a yeast-fermented liquor whose formula varies widely, and 'gaveen', which is a distillate of kaffir beer and shimiyane. Kaffir beer is a nutritious brew which has been shown sometimes to have a high iron content (Lamont, Gillman, and Hathorn, 1959). Shimiyane and gaveen are beverages containing a varying but high alcohol content. A feature of the African in giving his history is his extraordinary lack of reticence, and for this reason it is felt that the details of alcoholic consumption in 96 cases of porphyria given in Table IV are reasonably accurate. A similar comparison with 239 consecutive ward cases is made. Table IV suggests that patients with porphyria drank alcoholic beverages, particularly potent liquors, far more freely than the average patient found in a medical ward in this hospital.

Social background. Of the 100 patients, all but 11 were classifiable as pure Zulus (a branch of the Nguni group). Classification was based on the patient's own impression, surname, language spoken, and general physical characteristics. Of the remaining 11, eight were of Nguni origin other than Zulu (five Basuto, one Baca, one Boroka, and one Pondo). The remaining three patients were of mixed origin (one Griqua, one whose father was Indian and mother Zulu, and another possibly with distant European antecedents, but predominantly African). In 93 cases information as to whether the patient came from an urban or rural community was recorded. It was found that 80 patients (86 per cent.) came from urban areas, and 27 of these (29 per cent. of the total) came from Cato Manor, a slum area within the Durban boundary notorious for its squalor, alcoholism, and social and moral disruption (population approximately 100,000). This figure (29 per cent.) of cases from Cato Manor may be of significance when compared with the percentage of patients from the same area attending a consultative medical clinic of this hospital during 1958–60 (6·1 per cent. of 14,091 patients).

To summarize, patients suffering from porphyria who attended King Edward VIII Hospital appeared to consume diets better than the average, with a consumption of spirits greater than the average, and to hail mainly from urban, particularly slum, areas.

Family history. Ninety-four patients were carefully questioned as to whether any member of their family had at any time any of the obvious clinical features of porphyria in the African, particularly vesicles, hypertrichosis, and hyperpigmentation of the face. Ninety-one (97 per cent.) were emphatic that no such affliction was to be found in parents, sibs, or children. One patient stated that his mother had blisters similar in nature to those he was suffering from, and two other patients were mother and son, the mother (Plate 36, Fig. 4) suffering from leprosy, and the son (Plate 36, Fig. 5) almost certainly also suffering from leprosy (suspected on clinical grounds, though nerve biopsy and nasal scrapings were negative). These two patients freely admitted to being heavy shimiyane drinkers, their source of supply being the same. The mother had two other children, a daughter who had to the mother's knowledge no skin lesion of note, and a son who had died from unknown causes. Two other patients, sisters-in-law, but unrelated by blood, hailed from the same kraal in a rural area of Natal, and both had developed florid cutaneous lesions of porphyria at about the same time, as well as the same age (35 years). Both consumed the same brands of shimiyane and gaveen, and it was possible to collect from these patients samples of these liquors for experimental purposes.

Previous history of possible significance. Sixteen patients had been treated for amoebiasis at this hospital, where the routine therapy includes emetine, diodoquine, and chloroquine; two were receiving regular barbiturate therapy, one, an epileptic, taking phenobarbitone, and the other, a sufferer from asthma, taking a remedy containing amylobarbitone. Twelve had had surgical operations, during which anaesthesia was, according to the description by the patients, probably induced by thiopentone. Thus 30 patients may have been exposed to drugs such as barbiturates and chloroquine, which are known to aggravate porphyria in the genetic variety. Some of our patients related the onset of their lesions to exposure to these drugs.

B. *Physical examination*

Skin Lesions. Vesicles were present in 75 cases, either as unruptured blisters or as ulcers which had resulted from shedding of the pellicles of blisters. Forty-four were male and 31 female patients, and there appeared to be no difference in sex incidence. The vesicles were found mainly in areas exposed to light, especially on the backs of the hands and the fingers, on the lower legs and feet, and on the face (ears and forehead). Occasionally the blisters were extensive and confluent, especially in the extremities (Plate 36, Fig. 6).

Scars were present in 95 cases, and were most commonly situated on the backs of the hands (Plate 36, Figs. 4 and 5); sometimes they were evident only on close scrutiny. Two of the five patients in whom scars were not detected had blisters on admission, and three had neither blisters nor scars. One of the latter complained only of increased pigmentation of the face, and the other two had hyperpigmentation and hypertrichosis.

Onychia (blisters forming under the nail-beds of fingers or toes) was looked for in 91 patients (52 male and 39 female), and was found in 59 (65 per cent.).

It appeared to be slightly commoner in women, perhaps because they expose their hands more frequently to water.

Hyperpigmentation of the face was present in all 100 patients. Its characteristic blotchy nature helped to distinguish it from the diffuse, lack-lustre, grey-black pigmentation found in patients with advanced siderosis (Lamont, Gillman, and Hathorn, 1959). The patients often volunteered the information that this pigmentary change had paralleled the advent of other features of porphyria.

TABLE V

Liver Size in 100 Cases of Porphyria compared with 239 Consecutive Ward Cases

Liver size (finger-breadths)	*100 porphyria patients*			*239 consecutive ward patients* (%)
	Male	*Female*	*Total*	
Not palpable	2	4	6	33
1–2	34	23	57	50
3–4	21	13	34	17
More than 4	2*	1†	3	0
Total	59	41	100	100

* Both with primary carcinoma of the liver.
† Patient with leprosy (see Plate 36, Fig. 4).

Hypertrichosis of the forehead was recognized as extension of the hair-line down towards the brows; occasionally the hair, which was invariably dark and sometimes bluish and of delicate texture, was continuous between hairline and brow (Plate 36, Fig. 3). Not only was this feature of hypertrichosis found to be an easy means of recognizing cases of porphyria (particularly in women) but, almost without exception, hypertrichosis in this hospital means the detection of porphyrins in the urine. There was a difference in sex incidence in that 95 per cent. of women had hypertrichosis as against 56 per cent. of men. Hypertrichosis was also a valuable aid to the recognition of porphyria in female pellagrins. There were seven patients with concomitant pellagra (three male and four female); none of the male patients showed hypertrichosis, but all four female patients showed it to a marked degree.

Pellagra. Seven patients were suffering from pellagra as well as porphyria. There is normally a slightly higher incidence of pellagra in African women in the out-patient department of this hospital (57 female as against 45 male patients during 1958). It is our experience that alcoholism plays a more prominent aetiological role in female than in male patients, in whom a poor diet alone seems to predominate.

Fragility of the skin has been recorded as a feature of porphyria by Holti, Rimington, Tate, and Thomas (1958) and Eales (1960). Superficial abrasions and ulceration due to trivial trauma were found in 11 of our patients (10 male and one female). In our series we found it difficult to decide whether vesicles were due to photosensitivity or to trauma, and the decision often depended

on the observational powers of the patient rather than of the observer. We therefore recorded skin fragility as ulceration secondary to trauma but not obviously preceded by vesiculation.

TABLE VI

Nervous System Disorders in 58 Patients

	Male	*Female*	*Total*
Neuropathy (disturbed sensation, tender calves, absent or exaggerated reflexes, and hyperhidrosis)	26	22	48
Hyperhidrosis* (without neuropathy)	4	1	5
Epilepsy	2	1	3
Korsakoff's psychosis	2	0	2

* A striking feature when present, and described by all affected patients as being of recent onset.

TABLE VII

Plasma Iron, Total Iron-binding Capacity, and Haemoglobin in Complicated and Uncomplicated Porphyria

	Sex	*Number of cases*	*Plasma iron (μg./100 ml.) (mean ± S.D.)*	*Total iron-binding capacity (μg./100 ml.) (mean ± S.D.)*	*Haemoglobin (g./100 ml.) (mean ± S.D.)*
Uncomplicated porphyria	Male	33	245±55	321±59	16·4±1·4
	Female	22	201±73	281±51	14·8±1·3
Porphyria complicated by infections	Male	9	187±98	242±59	14·4±3·3
	Female	5	148±57	259±23	14·6±1·5
Porphyria complicated by pellagra	Male	3	126±38	239±92	15·7±1·2
	Female	4			
		7			

TABLE VIII

Plasma Iron, Total Iron-binding Capacity, and Haemoglobin in Porphyric Patients with Miscelllaneous Associated Conditions

	Number of cases	*Plasma iron (μg./100 ml.) mean (range)*	*Total iron-binding capacity (μg./100 ml.) mean (range)*	*Haemoglobin (g./100 ml.) mean (range)*
Cirrhosis	4	215 (144–337)	266 (147–322)	15·4 (11·0–17·8)
Cardiac failure	2	177 (97–258)	329 (308–50)	14·9 (14·6–15·2)
Carcinoma of liver	2	150 (138–63)	251 (191–312)	14·1 (13·2–15·0)
Diabetes	2	186 (168–204)	264 (208–320)	15·2 (14·6–15·8)
Lactating women	2	105 (72–138)	250 (201–300)	14·3 (12·9–15·8)
Hypertension	1	53	209	15·5

The size of the liver on palpation in our patients is shown in Table V. It will be seen that hepatomegaly was more prominent in patients suffering from porphyria than in the average patient in a general medical ward at this hospital, where the incidence of liver pathology is high (Wainwright, 1957; Gillman, Hathorn, and Lamont, 1958).

The spleen was palpable in 14 patients (seven male and seven female). It was 'tipped' or enlarged to one finger-breadth in two male and six female patients; larger spleens (two finger-breadths or more) were found in five male and only one female patient.

Hypertension. Of 90 cases in which the blood-pressure was recorded, the diastolic pressure was elevated in 25 (28 per cent.) to 100 mm. Hg or higher. It is doubtful whether this is of any special significance when compared with the general population of Africans in Durban (Scotch, Gampel, Abramson, and Slome, 1961). Hypertension has been described as a feature of the exacerbations of acute intermittent porphyria, but no oscillation in blood-pressure was observed to parallel changes in the clinical condition of our patients except in one male out-patient, in whom the initial blood-pressure was 235/135; three days later, with no special treatment, it had fallen to 140/90.

Nervous system. Seventy-three patients complained of subjective symptoms involving the nervous system. Objective evidence was found in 58 patients, of whom the details are shown in Table VI. In 55 of these 58 patients details of alcoholic consumption were available: in only one was complete abstinence claimed; seven drank kaffir beer only, and 47 (85 per cent.) drank spirits freely.

Laboratory Findings

Plasma iron, total iron-binding capacity, and haemoglobin were determined in 89 patients. The plasma iron level was over 200 μg. per 100 ml. in 45 patients (51 per cent.), and over 300 μg. per 100 ml. in 25 of these 45 cases, the normal range for plasma iron in our laboratory being 60 to 170 μg. per 100 ml. (Hathorn, Canham, and Gillman, 1960). The haemoglobin values were 13 g. per 100 ml. or less in seven patients, and above 17 g. per 100 ml. in 16.

Because infections and other associated diseases could have had an effect on plasma iron, total iron-binding capacity, and haemoglobin values, it was decided to analyse separately the results in 55 patients with porphyria not associated with other significant diseases ('uncomplicated porphyria'), in 14 patients with infections, and in seven patients with pellagra. The results are shown in Tables VII and VIII. Differences in means were associated by way of a two-tailed *t*-test, using the 5 per cent. level of significance. Of the 55 patients with uncomplicated porphyria, the men had significantly higher mean levels of plasma iron, total iron-binding capacity, and haemoglobin than the women. In addition, among the male patients, those with infections had significantly lower mean levels of plasma iron, total iron-binding capacity, and haemoglobin than those with uncomplicated porphyria; women showed similar trends, but the results were not significant, probably on account of the small number of female patients with infection. The mean plasma iron in the seven patients with pellagra was significantly lower than in the patients of both sexes with uncomplicated porphyria, although not significantly different from the value found in those with infections. Only one of these patients with pellagra had any notable infectious process (dry gangrene of the toes), and his plasma iron was 155 μg. per 100 ml. It was therefore improbable that infection was of any significance in accounting for the relatively normal levels of plasma iron in the patients with pellagra. Their mean total iron-binding capacity was significantly lower than that found in men with uncomplicated porphyria.

There was complete saturation of the total iron-binding capacity in 13 per cent. of all patients.

Serum bilirubin was measured in 95 cases; it was more than 0·8 mg. per 100 ml. in 23 out of 55 male and 12 out of 40 female patients, the highest value being 3·7 mg. per 100 ml.

TABLE IX

Serum Transaminase (G-OT) in 62 Patients with Porphyria

		Karmen units							
	Sex	*0–10*	*11–20*	*21–40*	*41–60*	*61–80*	*81–100*	*101+*	*Total cases*
Uncomplicated porphyria*	Male	3	1	3	4	5	0	4	20
	Female	0	3	3	9	3	0	3	21
Complicated porphyria	Male	0	1	4	3	2	1	2	13
	Female	0	3	1	3	1	0	0	8
Total	All cases	3	8	11	19	11	1	9	62

* Including patients with cirrhosis.

TABLE X

Serum Proteins in 96 Cases of Porphyria

		(Mean (range) in g./100 ml.)						
Test	*Number of cases*	*Albumin*	*Globulin*					*Total proteins*
Chemical	33	2·81 (1·6–4·4)	4·95 (3·4–7·8)					7·76 (5·0–10·3)
			α_1	α_2	β	γ		
Electrophoresis		2·61	0·62	1·1	1·35	2·75		8·43
	63	(1·6–3·8)	(0–1·3)	(0·8–1·6)	(0·7–2·1)	(1·8–6·1)		(6·9–10·3)
			5·82					

Alkaline phosphatase was measured in 95 cases. One patient had a level less than 3 King–Armstrong units; in 51 patients it was greater than 10 King–Armstrong units, the highest level recorded being 30 units. There was no noticeable sex difference.

Serum glutamic-oxalacetic transaminase (G-OT) was estimated in preference to glutamic-pyruvic transaminase (G-PT) because the incidence of myocardial infarction in Africans in this hospital is so low that it does not raise problems of differentiation, and estimation of G-OT activity was more convenient. The results in 62 patients are shown in Table IX, and suggest that elevation of serum G-OT activity is common in African patients with porphyria (64 per cent. had levels above 40 Karmen units). In all three cases falling in the range 0 to 10 units there was gross liver disease, confirmed histologically—cirrhosis in two, and a primary carcinoma of the liver in one. In this laboratory the normal range found in Africans is 10 to 40 units (Joubert, 1960). Thus 43 patients (69 per cent.) had serum G-OT activity outside the normal range.

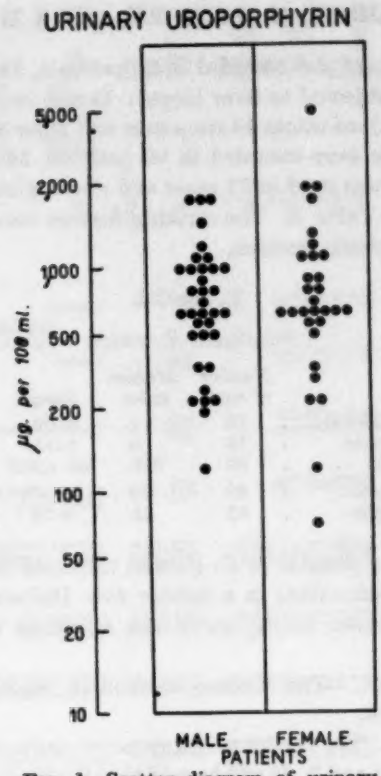

FIG. 1. Scatter diagram of urinary uroporphyrin concentration in 35 male and 30 female patients (logarithmic scale).

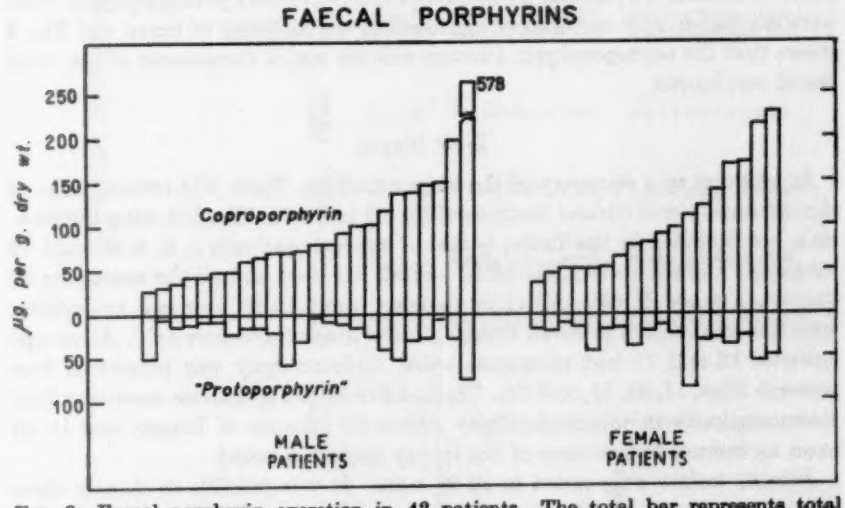

FIG. 2. Faecal porphyrin excretion in 42 patients. The total bar represents total porphyrins; the portion above the line in each case representing coproporphyrins, and that below the line the non-coprophyrin fraction. In a further 11 male and nine female patients the screen test was negative, the results being omitted from this figure.

The prothrombin index was recorded in 50 patients, 34 male and 16 female, including all those subjected to liver biopsy. It was below 70 per cent. in 13 patients (26 per cent.), of whom 10 were men and three women.

Serum-protein levels were recorded in 96 patients, 56 male and 40 female. Chemical estimation was used in 33 cases and electrophoresis in 63. The findings are recorded in Table X. The striking feature was hyperglobulinaemia, especially in the γ-globulin fraction.

TABLE XI

Porphyrin Excretion

		Number of cases	*Median value*	*Range*	
Urine	δ-aminolaevulic acid .	16	4	0–22	(μg./l.)
	Porphobilinogen .	16	0	0–15	(μg./l.)
	Uroporphyrin . .	65	650	68–4,962	(μg./100 ml.)
Faeces	Coproporphyrin . .	62	50	0–578	(μg./g. dry weight)
	Protoporphyrin . .	62	15	0–74	(μg./g. dry weight)

Blood sugar. It was possible to do glucose tolerance tests in 17 cases, and fasting blood-sugar estimations in a further five. Diabetes was found in one patient; in the remainder fasting levels and responses to oral glucose were normal.

Wassermann reaction. The Kolmer cardiolipin reaction was positive in 31 per cent. of patients.

Porphyrin excretion. The results of quantitative estimations are summarized in Table XI and Figs. 1 and 2. It will be seen that the precursor levels (δ-aminolaevulic acid and porphobilinogen) were not appreciably elevated in any of the patients studied. Uroporphyrin levels were over 500 μg. per ml. in 48 of the 65 patients studied (74 per cent.). Faecal coproporphyrin and protoporphyrin levels were normal or only moderately increased in the majority of cases, and Fig. 2 shows that the coproporphyrin fraction was the major component of the total faecal porphyrins.

Liver Biopsy

In addition to a summary of the biopsy findings, Table XII reflects some of the laboratory and clinical features of the 28 patients. The following information, not included in the Table, is also of interest: patients 2, 5, 9, 20, and 72 consumed a grade I diet, patient 80 a grade III diet, and all the remaining 22 patients a grade II diet. All these patients drank kaffir beer and raw spirits, with the exception of patients 10 and 11, who drank kaffir beer only. All except patients 12 and 79 had cutaneous scars. Splenomegaly was present in four patients (Nos. 13, 32, 53, and 72). The last five biopsy specimens were examined macroscopically in ultraviolet light within 30 minutes of biopsy, and in all cases an intense fluorescence of the biopsy cores was noted.

Fibrotic lesions were noted in all 28 cases. It was possible to classify these lesions into three broad categories, namely periportal fibrosis, intralobular

TABLE XII

Clinical, Biochemical, and Biopsy Findings in 28 Patients with Porphyria

KC = Kupffer-cell iron.
HC = Hepatocellular iron.
P = Periportal iron.

Case number	Age (years)	Sex	Vesicles	Hypertrichosis	Blood and plasma: Haemoglobin (G./100 ml.)	Prothrombin index (%)	Serum bilirubin (mg./100 ml.)	Alkaline phosphatase (King–Armstrong units)	Plasma iron (µg./100 ml.)	Total iron-binding capacity (µg./100 ml.)	Serum G-OT (Karmen units)	Urinary uroporphyrin	Faecal porphyrin: Copro	Faecal porphyrin: Proto	Liver biopsy: Fat	Liver biopsy: Bile-duct hyperplasia	Liver biopsy: Iron
A. *Portal fibrosis*																	
1	60	F	0	+	14·3	100	<0·8	13	106	215	..	..	..	..	Slight	0	Nil
14	40	M	+	0	19·5	95	<0·8	14	267	212	..	..	..	..	,,	0	KC
15	43	M	0	0	16·3	58	<0·8	13	212	271	..	..	..	..	,,	0	Nil
44	50	M	+	+	16·0	69	0·9	10	256	341	110	330	80	7	+	+	KC, P
52	49	F	0	+	13·5	86	1·6	14·8	182	292	18	242	50	43	0	+	KC
B. *Intralobular fibrosis*																	
3	49	F	+	+	16·4	88	<0·8	12	..	..	..	..	..	..	0	0	KC
5	33	M	+	+	16·2	82	<0·8	11	300	449	..	..	..	..	+	0	HC, KC
8	42	M	0	+	16·2	100	<0·6	12	208	200	..	..	..	..	Slight	0	HC, KC
10	32	M	+	0	19·1	93	1·3	13	272	262	..	..	..	..	,,	0	KC
20	36	F	+	+	14·4	70	1·2	15	214	294	120	340	79	20	,,	0	KC
53	42	M	+	+	14·6	100	0·3	3	176	306	6	600	78	31	Slight	0	HC, KC
63	34	F	+	+	16·8	79	0·3	8	162	223	20	615	141	28	0	0	HC, KC
72	35	F	+	+	16·0	69	0·7	10	107	331	50	123	122	31	0	0	Nil
80	47	M	+	0	17·1	82	0·9	10	274	329	40	801	0	0	+	0	Nil
81	38	M	+	0	15·5	92	0·8	6	84	186	84	255	0	0	+	0	KC
86	56	M	+	0	17·0	70	1·2	7	180	288	20	502	35	12	0	+	HC, KC, P
C. *Cirrhosis*																	
2	52	M	+	+	9·6	77	1·8	8	101	190	..	..	..	..	0	+	HC, KC
4	47	M	0	+	15·8	77	<0·8	..	..	..	..	..	..	..	0	++	P
6	38	M	0	+	16·2	82	1·4	9	346	325	..	..	..	..	0	+	KC
7	37	M	+	+	15·6	78	1·1	12	255	245	..	..	..	..	Slight	0	KC
9	34	M	0	+	15·9	80	<0·8	20	292	334	40	..	..	..	,,	0	KC
11	51	M	0	0	14·8	73	1·2	15	238	296	..	..	..	..	+	0	KC
12	48	M	0	0	17·0	74	<0·8	8	245	359	..	..	..	..	Slight	0	KC
13	40	M	+	0	15·5	92	0·9	10	338	337	..	..	..	..	,,	+	KC, P
32	59	M	+	+	14·9	69	<0·8	13	190	200	..	500	69	19	0	0	KC, P
47	70	M	+	0	18·0	61	<0·8	15	189	200	66	415	0	0	0	0	KC
65	44	M	0	0	17·2	100	1·0	9	337	272	80	243	92	11	0	0	P
79	64	F	0	0	15·8	66	2·3	18	204	308	60	266	0	0	Slight	+	KC

fibrosis, and cirrhosis (see Table XII). Five cases showed periportal fibrosis, with increase in periportal connective tissue and reticulin (Plate 37, Fig. 7). In two of these cases there was marked portal cellularity, while the other three showed slight cellular infiltration. In 11 cases the predominant lesion was the presence of abnormal fibrous tissue within the liver lobules. This took the form either of discrete aggregations of connective tissue scattered throughout the lobule (five cases) or of a tendency for these areas to link up, dividing the liver lobule by bands or septa of connective tissue (Plates 37 and 38, Figs. 9, 13, and 14). The 12 cases designated as cirrhosis appeared to be more severe examples of the intralobular fibrosis just described, but with more pronounced disorganization of lobular structure, and the presence of hyperplastic nodules (Plate 39, Figs. 15, 17, and 18). In view of the prevalent confusion in the classification no attempt has been made to label the type of cirrhosis found in these cases. It was clear, nevertheless, that none of these patients showed the type of 'portal' cirrhosis associated with heavy portal iron deposits found in Durban Africans (Gillman, Hathorn, and Lamont, 1958), nor did they show the broad bands of scar tissue characteristic of post-necrotic scarring. Instead, they exhibited some of the features of livers variously described as examples of 'septal' or 'Laennec's' cirrhosis. A few loci of acute cellular necrosis were found in 3 cases. Anisocytosis and vacuolation of the cytoplasm were found in a number of the cases of cirrhosis.

Moderate *fatty change* was present in four cases (Plate 38, Fig. 14), while smaller amounts were found in a further 12 patients (Plates 37 and 39, Figs. 9 and 16). In the remaining 12 cases no fat was demonstrable. In no case was fatty change as marked as that usually associated with alcoholic cirrhosis occurring elsewhere, in spite of the considerable consumption of alcohol by our patients.

Staining for *iron* showed that iron was virtually absent in four cases. In 16 cases (see Table XII) iron was predominantly in Kupffer cells, either singly (Plate 39, Fig. 16) or in coarse clumps (Plate 38, Figs. 11 and 12) with only traces of hepatocellular or portal-tract iron. In two cases both hepatocellular and Kupffer-cell iron was notable; in four cases both Kupffer-cell and portal-tract iron was predominant (Plate 37, Figs. 8 and 10), while in the remaining two cases the iron was confined mainly to the portal tract. In none of these cases was iron accumulation as heavy as is often found in many Africans with hepatic siderosis; these cases of porphyria also differed from those of siderosis in that the iron was predominantly reticulo-endothelial, as compared with the hepatocellular distribution usually found in siderosis in Africans, especially in the early stages.

Bile-duct hyperplasia was found in eight cases, but without exception it was of mild degree. In was associated in most cases with elevated serum-bilirubin levels (Table XII).

Post-mortem liver specimens. Case 32, one of those in which a liver biopsy had been performed (Table XII), showed the same histological features as had been noted on biopsy. The other patient from whom a specimen of liver was obtained

at necropsy had a well-marked cirrhosis of the liver, with moderately heavy iron deposits in the portal tracts and in clumps of intralobular Kupffer cells.

Discussion

We owe our present status of knowledge of porphyria as it affects both the African and the white South African to the meticulous studies of Barnes (1959) in the first place, and latterly to Dean and Barnes (1959) and Eales (1960). It is interesting that the first descriptions of porphyria in South Africa came from the veterinarians (Fourie, 1936; Fourie and Rimington, 1938). These writers recorded the presence of 'pink tooth' and photosensitive skin lesions in association with pathological excretion of porphyrins, and were able to establish definite genetic relationships in the cattle described. The first cases described by Barnes (1945) included five Africans and six white South Africans. While the latter all presented acute abdominal or psychological disturbance, none of the Africans showed these features, and all except one had well-marked cutaneous lesions. These skin lesions appeared to be diagnosed as atypical pellagra by the clinical observers of Barnes's cases.

Difficulties persist in the *classification* of porphyria, and particularly of the disease as it affects the African, and will probably continue until our knowledge regarding the fundamental mechanisms is more accurate. Watson (1959–60), in referring to the various sub-groups of the hepatic variety, commented on a recent paper by Barnes (1959) on porphyria in the African. Watson stated: 'Further study is necessary to determine the exact differences and the extent to which they are genetically determined or related to factors of climate or environment.' There seems little doubt that porphyria in the African falls into the category of the hepatic variety, and that the acute intermittent sub-group is rare. Although isolated cases of acute intermittent porphyria have been reported in Africans (Woods and Barnes, 1951), none were examined adequately in the laboratory until Barnes, Neser, and Popper (1960) made the first detailed study. In this most recent case, however, heredity was not established. Other reports (for example, Gelfand and Mitchell, 1957) subscribe to the view that porphyria in the African falls predominantly into the chronic cutaneous sub-group of the hepatic variety. This term is preferable to the term 'cutanea tarda', as cases of hepatic porphyria have been reported with onset in childhood (for example, those of Barnes, Frootko, and Parnell, 1957). No case in the present series bore any clinical resemblance to the acute intermittent variety.

Clinical picture. The *cutaneous lesions* in our patients appeared remarkably uniform in their presentation. They ranged from florid to chronic skin lesions. We have not studied our material for long enough to be able to record any possible correlation between cutaneous lesions and porphyrin excretion; nor have we observed our patients long enough from the clinical point of view to have a clear-cut concept of the natural history of the disease in the African. It appears, however, that the African may have one or more episodes of florid skin lesions, with vesicles, ulcers, and onychia prominent, followed by a chronic

state in which hyperpigmentation, hypertrichosis, and scars are evident. Whether or not a stage is reached when no further bullous episodes supervene is not yet clear, and only further study will answer this question.

The recently published descriptions of the cutaneous lesions in cases of 'toxic porphyria' emanating from Turkey (Cetingil and Özen, 1960; Schmid, 1960) resemble closely the cutaneous lesions found in our patients—the hyperpigmentation and hypertrichosis, the vesicles, and the scars. Whereas hypertrichosis was prominent in all the Turkish patients described (the majority of whom were children), in our series it was predominantly found among women. It is of interest that the two women who did not have hypertrichosis both developed their porphyric symptoms after the menopause, one after the age of 65 years. It is possible that hypertrichosis may be an endocrine manifestation. As in the description of Turkish cases of 'toxic porphyria', abdominal symptoms were not prominent in the present series. Hepatomegaly was conspicuous in our patients, and was recorded by Schmid (1960) in his Turkish patients. The majority of our 58 patients with abnormalities of the nervous system suffered from peripheral neuritis. It is of interest that this was not a feature of the Turkish cases; this fact adds weight to the suggestion that in our patients alcoholism was probably an important factor in the development of peripheral neuritis. Psychoneurotic symptoms were singularly absent, whereas they are prominent in variegate porphyria in white South Africans and in the acute intermittent porphyria of Waldenström. Our analysis of the personal habits of our patients shows that alcoholism plays a prominent part in the social background of a high proportion of patients suffering from porphyria. Their diets (grade II), although slightly better than the average, were still far from adequate.

Laboratory findings. The lesions of the liver in biopsy and post-mortem material suggest a chronic rather than an acute process. This is borne out first by the presence of fibrotic lesions in all the cases examined, and secondly by the paucity of evidence of acute necrosis. On the other hand, the six Turkish patients who were subjected to liver biopsy (Cetingil and Özen, 1960) all had parenchymal degeneration of the liver cells. The biochemical tests of liver function do not reflect a uniform picture. In view of the fact that some patients suffered from diseases unrelated to porphyria, and that single examinations were carried out at various stages of the disease in different patients, uniformity could hardly be expected. In some patients impaired excretory function of the liver was suggested by increased alkaline-phosphatase activity and raised serum-bilirubin concentration. The latter finding was associated with bile-duct hyperplasia on biopsy. The increased transaminase activity in 64 per cent. of patients can only be interpreted as evidence of active hepatocellular damage at the time of examination, because there was no clinical evidence of myocardial or skeletal muscle disease which could give rise to comparable increases. It is well established that there are differences of serum-protein pattern between white subjects and apparently healthy Africans (Joubert, Hookins, and Hunter, 1959). The albumin levels in our porphyria patients did not differ materially from those described in Durban Africans, but all globulin fractions in our

patients were markedly increased. All these findings are fully compatible with the presence of liver disease.

The excretion of porphyrin and porphyrin precursor in our patients was closely similar to that found by Barnes (1959) in Johannesburg. Characteristically, the excretion of δ-aminolaevulic acid and porphobilinogen in the urine is very small, whereas the total porphyrin content of the urine is grossly excessive. Faecal excretion of coproporphyrin and protoporphyrin (the non-coproporphyrin fraction) is within normal limits or moderately increased. The most outstanding characteristic in the faecal excretion, in our view, is the predominance of coproporphyrin, whereas normally, and in all other recorded forms of porphyria, the protoporphyrin fraction predominates. From the data in the present study no correlation was found between the excretion of porphyrin and porphyrin precursor and the clinical presentation. From limited observation on recent examinations of some patients, we found that there was considerable day-to-day variation. More closely controlled studies will have to be undertaken to establish whether the excretory pattern is related to the clinical course of the disease. We emphasize the fact that our clinical and laboratory findings establish beyond all reasonable doubt a definite entity different from protocoproporphyria (Waldenström's porphyria cutanea tarda hereditaria).

The elevated levels of plasma iron in our patients are difficult to interpret, as are the relatively normal values in those who were suffering from concomitant pellagra. Large increases in plasma iron have been reported in patients with haemochromatosis and transfusion siderosis (Rath and Finch, 1949), in some African patients with dietary siderosis (Hathorn, Gillman, Canham, and Lamont, 1960), in certain types of anaemia, after iron administration, and in acute infectious and toxic liver lesions. In the last-named conditions it has been suggested that the high plasma-iron levels are due to the release into the circulation of iron from the damaged liver cells, some possibly in the form of ferritin. In these cases the hypersideraemia is usually short-lived, and normal levels are reached after a short period. In our porphyria patients, on the other hand, the high plasma-iron levels were usually sustained over considerable periods; for example, one patient followed up for 12 months had successive levels of 214, 208, 208, and 252 μg. per 100 ml. In spite of the fact that 24 of our 28 patients subjected to biopsy had demonstrable siderosis, three of the four with no siderosis had high plasma-iron levels. This finding suggests that the hypersideraemia in many of our patients may have been unrelated to excessive iron stores in the liver. On the other hand, the reticulo-endothelial predominance of iron in our biopsy material, as distinct from the predominantly hepatocellular distribution in siderotic Africans without porphyria, suggests that in the former the more easily available hepatocellular iron has already been mobilized. As will be mentioned below, the possibility exists that our patients had repeated episodes of mild toxic hepatitis, which could result in the frequent release into the plasma of iron from liver stores. The precise relationship between elevated plasma-iron levels and disturbances in porphyrin biosynthesis thus seems to be obscure. Further studies of the iron turnover in porphyria in the African,

along the lines reported by Keeley, Bothwell, and Kramer (1960), are clearly required.

Two facts related to porphyria in the African are of special interest. First, available evidence has always suggested that the disease is acquired. Secondly, porphyria is a comparatively common disease in Africans. While it is possible that a genetically transmitted form of porphyria may occur in the African, there is now overwhelming evidence that in the vast majority it is an acquired disease. The obvious question is: how is the disease acquired? Apart from the uniform clinical picture in African patients, a notable feature is the associated liver disease. Earlier investigators have realized this, but the state of the liver has so far received scant attention. Our findings do not point to any specific type of liver disease, but it is relevant to draw on local experience. In an investigation into the frequent occurrence of spontaneous hypoglycaemia in the African, Neame and Joubert (1961) have established that ethyl alcohol acts as a specific hepatic toxin in poorly nourished subjects, giving rise to a 'toxic hepatitis', with transient bilirubinaemia and increased serum alkaline phosphatase and transaminase (G-OT) activity. Biopsy material at this stage showed no histological evidence of liver-cell necrosis. This action of ethyl alcohol is similar to, though not necessarily identical with, the findings in chronic alcoholics (Bang, Iversen, Jagt, and Madsen, 1958; Hed, 1959). The prerequisite for its toxic action appears to be poor nutrition, although the nature of the protection given by an adequate diet is at present not known. In view of the alcoholic and dietary histories of our patients, it is reasonable to infer that ethyl alcohol may similarly have acted as a toxin in our patients, and our biochemical tests of liver function conform with this view. It should be appreciated that our patients are not chronic alcoholics in the accepted sense, but rather heavy week-end drinkers.

If this view has substance, we conceive the process as being one of repeated episodes of mild toxic hepatitis occurring over a considerable period. From this point of view the Turkish experience is of great interest. In these patients the clinical manifestations were closely similar to those we have reported, gross liver disease was an invariable concomitant, and, biochemically, the derangement in porphyrin metabolism appears to have been similar. More important, however, is the fact that the Turkish group is the first large-scale example of acquired porphyria in man unequivocally due to a known aetiological agent. Porphyria in the Turkish patients has been shown to be due to the prolonged action of the hepatic toxin hexachlorobenzene; it is conceivable that porphyria in our patients may similarly have followed the consumption of ethyl alcohol in a particular dietary setting. In our view it is not necessary to postulate hypothetical toxins in the brews and distillates consumed by the African patients now that it is known that ethyl alcohol can act as a hepatic toxin. On the other hand, it cannot be denied that our patients may have had access to other unidentified toxic substances, but no evidence to this effect has been forthcoming. The liver has been suggested as the site of abnormal porphyrin synthesis in our patients. Whether liver disease is the cause of this abnormal

porphyrin metabolism, or whether abnormal porphyrin synthesis is independent of the liver disease, and its excretion merely modified by hepatic malfunction, is not yet clear. While our hypothesis is far from proved, we consider it may be of value in suggesting a controlled experimental approach to the problem.

We record our gratitude to Professor T. Gillman for his encouragement, and for his assistance in collecting the biopsy material; Professor J. Wainwright for his assistance; Dr. P. A. S. Canham for the plasma-iron determinations; Mrs. P. Kruger for histology and photography; Miss M. N. Dick for laboratory assistance; and Miss M. Carolan and Mrs. J. Rudder for secretarial assistance. We also wish to thank Dr. A. J. Wilmot, of the Department of Medicine, and Dr. S. Disler, of King Edward VIII Hospital, for permission to publish this report. This investigation was aided by a grant from the National Institutes of Health, United States of America.

Summary

1. We have examined 100 Africans suffering from 'chronic cutaneous porphyria'. There were 59 male and 41 female patients, and 97 per cent. were of Nguni origin. Our cases conformed to the clinical and biochemical pattern originally described by Barnes (1959).

2. Most patients showed cutaneous bullae, scars, hyperpigmentation, and hypertrichosis. Examination usually showed the liver to be enlarged, and signs of peripheral neuritis were present in half the patients. Abdominal symptoms, when present, were apparently unrelated to porphyria.

3. The symptoms of porphyria in the African are often benign and incidental to other diseases. The duration of symptoms attributable to porphyria in the majority of patients was less than two years; they consumed predominantly maize diets, and drank raw spirits to excess. All gave a history of having passed 'red' urine.

4. Liver biopsies were performed in 28 of these patients, and specimens of liver were obtained *post mortem* from two patients who had died of other diseases. All cases showed fibrotic lesions of the liver. Most of the livers showed the presence of iron, but its extent and distribution differed from that usually found in Africans in this country.

5. The pattern of porphyrin excretion closely resembled that described by Barnes (1959) in Africans, in that urinary uroporphyrins predominated. Other laboratory investigations suggested the presence of liver disease in all the patients. Haemoglobin levels were normal or elevated, and plasma iron was considerably increased in the majority of cases.

6. Clinically, and probably biochemically, our cases closely resemble the recently described Turkish group, in which hexachlorobenzene has been incriminated. Although the aetiology of the condition in our cases is not known

with certainty, there is no evidence to suggest a genetic origin. It is suggested that porphyria in the African is an acquired condition, and may follow the consumption of ethyl alcohol in a particular dietary setting.

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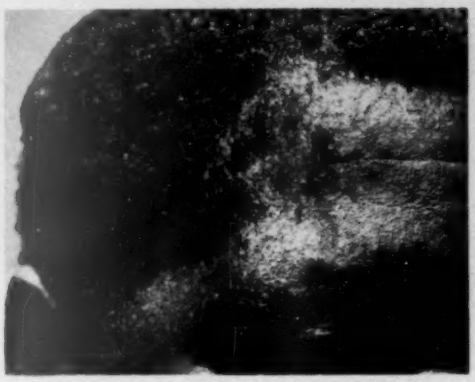

FIG. 3. Hypertrichosis in an African woman with porphyria. Note encroachment of the hair-line towards the eye-brow

FIG. 4. A female patient with porphyria and leprosy. Note the porphyric scars on the hand and the leprous macules

FIG. 5. Porphyric scars on the hands

FIG. 6. A large vesicle on the foot of the patient shown in Fig. 3

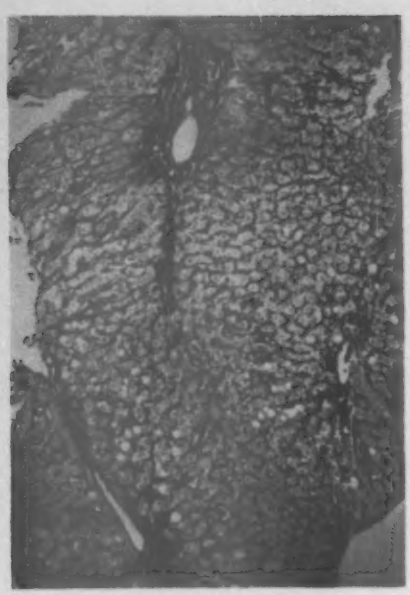

FIG. 7. Liver biopsy specimen from a case of porphyria showing periportal fibrosis (reticulin stain, × 52)

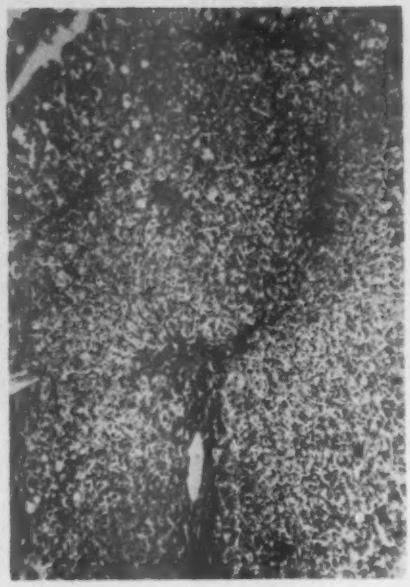

FIG. 8. The same case as Fig. 6 showing scanty iron-staining material round portal tract and in intralobular Kupffer cells (iron stain, × 52)

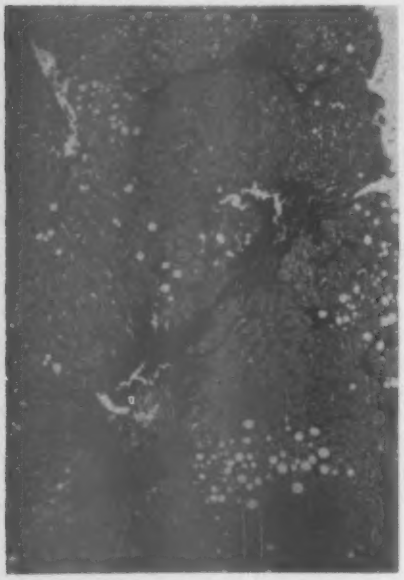

FIG. 9. Liver biopsy specimen showing periportal and intralobular fibrosis, and mild fat accumulation (reticulin stain × 52)

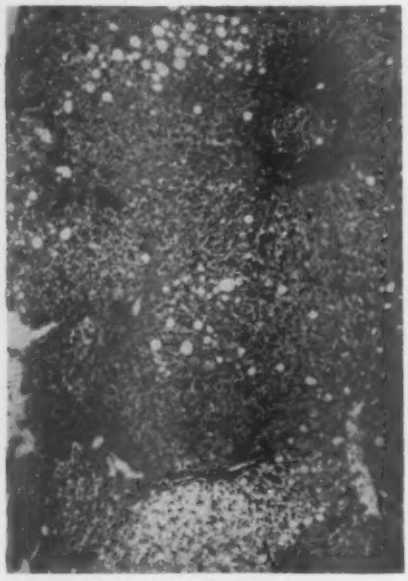

FIG. 10. Serial section of Fig. 9 showing clumped iron in Kupffer cells and portal phagocytes (iron stain, × 52)

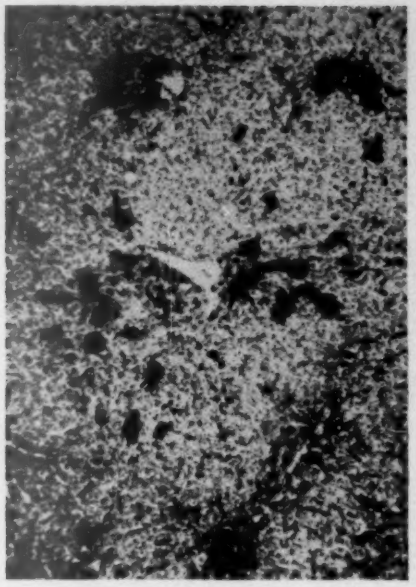

FIG. 11. Heavy clumping of iron scattered throughout liver lobule. This was the most siderotic case in the whole series (iron stain, ×52)

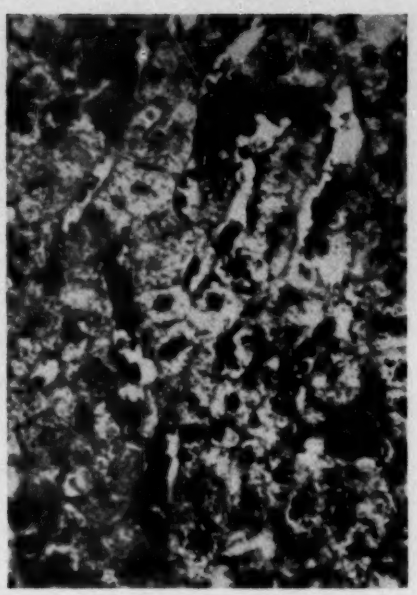

FIG. 12. High-power view of Fig. 11 showing clumping of iron in Kupffer cells and traces of hepatocellular iron (iron stain, ×350)

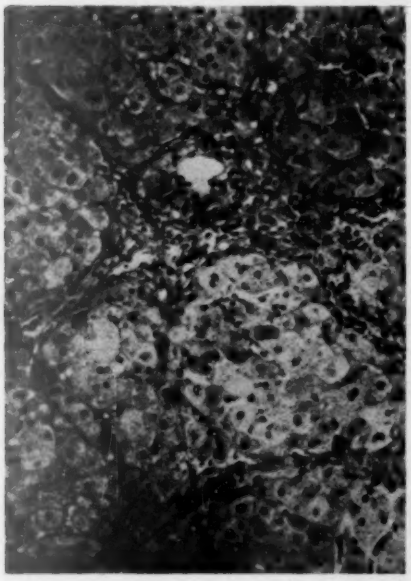

FIG. 13. Liver showing intralobular fibrosis (Masson stain, ×140)

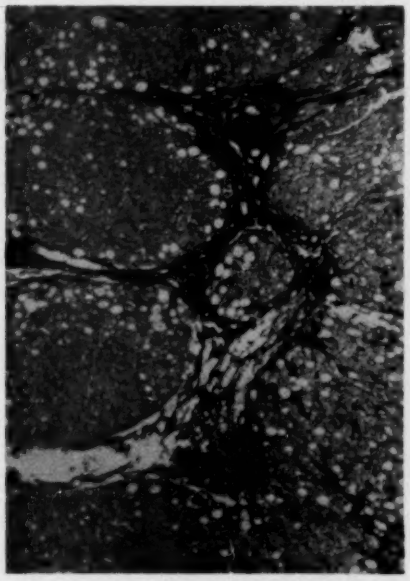

FIG. 14. Liver showing intralobular and some periportal fibrosis, and mild fat accumulation (reticulin stain, ×70)

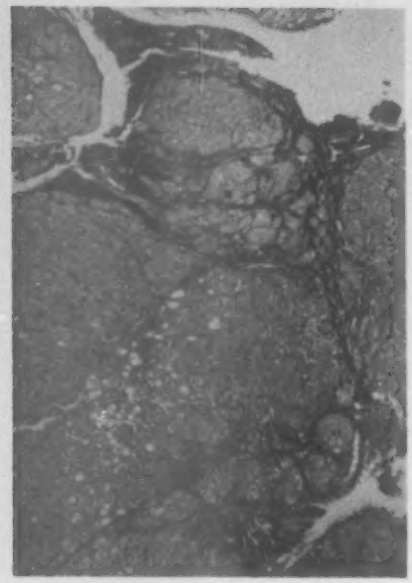

FIG. 15. Liver showing cirrhosis (reticulin stain, × 52)

FIG. 16. Serial section of Fig. 15 showing mild reticulo-endothelial iron accumulation (iron stain, × 52)

FIG. 17. Liver showing cirrhosis (Masson stain, × 70)

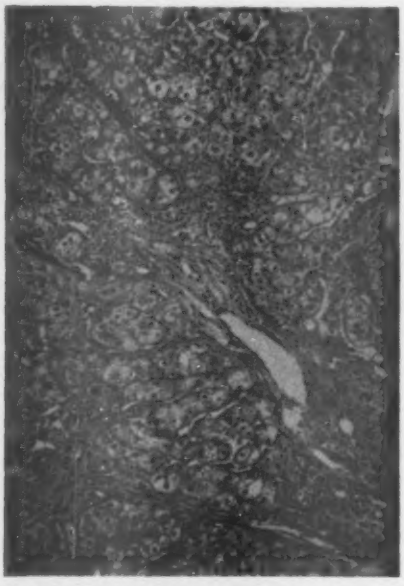

FIG. 18. High-power view of Fig. 17, showing fibrous tissue and alterations in morphology of liver cells (Masson stain, × 118)

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THE VALUE OF RECTAL BIOPSY IN THE DIAGNOSIS OF ULCERATIVE COLITIS[1]

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With Plates 40 to 42

INTRARECTAL methods have been employed in the diagnosis of ulcerative colitis for many years. Sigmoidoscopy is safely carried out as a routine in patients suspected of suffering from any disease of the large bowel or rectum. It has been said that 95 per cent. of cases of ulcerative colitis in an active phase will show changes in the rectum or lower sigmoid colon on careful examination with a sigmoidoscope (Bargen, 1935; Bockus, 1944–6). Other authorities have refuted this figure, and some have suggested that the percentage should be lower because the disease does not start in the rectum in this percentage of cases (Turell, 1959). An analysis of 124 cases of acute and subacute ulcerative colitis seen by the present writer has shown that in 116 (93·5 per cent.) definite sigmoidoscopic changes were found in the rectal or lower sigmoid mucosa. This result certainly seems to support the diagnostic value of sigmoidoscopy in the acute or subacute phase of the disease. In the chronic or quiescent stages of ulcerative colitis there is less likelihood of finding such changes. The sigmoidoscopic appearances referred to are well known, and have been fully investigated and described by other observers. The present writer has analysed the results of more than 500 sigmoidoscopies personally performed in cases of ulcerative colitis, confirming the accuracy of those descriptions and also the wide range of variation shown by the mucosal changes in this disease.

Barium-enema studies are another valuable adjunct to the diagnosis of ulcerative colitis. There is little doubt, however, that in many cases they give a normal appearance although active disease is present. Analysis of the barium-enema studies undertaken on the first 50 patients (unselected) who attended a special clinic for the study of ulcerative colitis reveals a positive finding in 35 and a normal result in 15. The diagnosis of ulcerative colitis was confirmed by other means in all cases. This finding supports the belief that the barium enema may yield a high percentage of normal results in a cross-section of patients with various degrees and types of ulcerative colitis. The changes found on barium examination of the colon will not be reported in detail, as they have been fully investigated and described in the past.

[1] Received February 17, 1961.

It is clear that the above diagnostic methods are of great value. In some cases, however, both give normal findings in the presence of disease. In an endeavour to close this gap in diagnosis an investigation has been undertaken of the value of rectal biopsy.

Rectal Biopsy

Historical. Biopsy of the rectum, as an aid to diagnosis of various diseases, has been recorded occasionally during the past 60 years. The first serious study was undertaken in 1931 by Gabriel. He reported the results of rectal biopsy as an aid to the diagnosis of malignant disease and obscure granulomatous lesions, and recommended its use in those conditions. Since then it has been widely used in this connexion (Gabriel, Dukes, and Bussey, 1951). Rectal biopsy was described as an aid to the diagnosis of schistosomiasis in 1943 (Ottolina and Atencio), and of amoebic dysentry in 1944 (Craig). Little mention of its use in ulcerative colitis occurred until 1951, when Levine, Kirsner, and Klotz described some results in this disease. Truelove, Horler, and Richards (1955) reported a simple method of obtaining biopsy material from the rectal mucosa, and described the histological findings in ulcerative colitis. Lumb and Protheroe (1955), using a different method of removing the pieces of rectal mucosa, also reported their results in a series of cases. There has been only one further British publication relating to biopsy in ulcerative colitis (Truelove and Richards, 1956).

Methods available. Many different methods have been used to obtain specimens of rectal mucosa for histological examination. Spingarn, Edelman, Gold, Yarnis, and Turell (1957) employed a bladder punch or rigid angulated cutting forceps, but, owing to the possible dangers of either perforation or excessive bleeding, limited the site of biopsy to the rectal valves. Cropper (1945) also used a method of punch biopsy, but this again was shown to have some dangers. Manson-Bahr and Muggleton (1957) used a Volkmann's spoon to scrape off a specimen of rectal mucosa, but were mainly interested in finding amoebae, and could disregard the inevitable trauma and distortion of the mucosal architecture which this method involved. Lumb and Protheroe (1955) used Officer's forceps for biopsy, but limited the operation to projecting folds of mucosa. They stated that it is technically easier to obtain specimens by this method. Juniper, Steele, and Chester (1958) used a Turrell or Welch–Allen rectal biopsy punch forceps, but restricted the site of biopsy to the middle of the valve of Houston because of the risk of perforation. Craig (1944) used either a Volkmann's spoon or a curette, but the mucosa was often severely damaged and the cellular architecture spoiled by this method. There are several other instruments in fairly common use. These include Brüning's forceps, which does not secure a very good mucosal specimen, and also can be very traumatic to the rectum; ordinary alligator forceps, mainly used for removal of pieces of a rectal neoplasm; and modifications of Hartmann's conchotome, which usually damages the mucosa, distorting the cellular architecture. All these instruments carry a slight risk of complications, and do not

produce a very good histological specimen for the study of the mucosal pattern. Truelove, Horler, and Richards (1955), however, used a simple method of suction biopsy, which had no restriction as to site of employment and appeared to offer little chance of dangerous complications.

Methods selected. Methods which restrict the site of biopsy for either technical or safety reasons are not really satisfactory, as one may possibly get a false picture of the pathological changes, which may differ from one area of the rectum to another. Biopsy techniques which may damage or distort the specimens are also unsatisfactory if an accurate and careful study is to be made of all aspects of the specimens. After consideration, a modified version of the Truelove suction-biopsy apparatus was selected, as it seemed to offer the greatest versatility in use, was probably the safest instrument, and would yield undamaged specimens for histological examination. A Coldlite type sigmoidoscope was specially modified for use with this instrument to give the optimum lighting conditions and, because of the absence of a light carried in the lumen, to give the maximum working space for use in biopsy. In order to be prepared to cauterize any areas of excessive bleeding, a special long clamp probe was designed which could carry either a chemical or an electrical cautery to all areas of the rectum or lower sigmoid. It was then felt that the selected method would be safe, simple to use, able to supply useful material, and unlikely to be followed by dangerous complications.

Technique. No preparation, premedication, or anaesthesia was found to be necessary, and most of the subjects were out-patients who returned home quite happily after biopsy had been undertaken. The patient was placed in the left lateral position and the special Coldlite sigmoidoscope passed. Careful examination by sigmoidoscope was first undertaken, to obtain a full picture of the local disease and to rule out any other lesion. The sterilized biopsy instrument was then assembled for use, and introduced through the lumen of the sigmoidoscope into the rectum. Under direct vision a suitable area was selected for biopsy, and the small hole in the side of the head of the instrument placed in apposition to this area. Suction by hypodermic syringe through the plastic tube was then carried out by an assistant until some resistance was felt to withdrawal of the barrel of the syringe, indicating that an area of mucosa had occluded the small hole in the biopsy instrument. The central rod operating the small internal guillotine was then rapidly depressed, and the mucosal specimen cut off but retained inside the head of the instrument, which was then withdrawn, and the mucosal specimen transferred to a pot containing formol saline. The site of the biopsy was then inspected for any signs of excessive trauma or bleeding. Bleeding always appeared to cease in less than five minutes.

At the time of biopsy the full details of the symptoms, signs, and sigmoidoscopic findings were recorded. Blood was also taken for estimation of haemoglobin and erythrocyte sedimentation rate, so that the clinical picture could be correlated with the histological changes.

Complications. No complications were found in the 126 cases. Three patients complained of excessive bleeding on the next occasion when their bowels acted after the biopsy, but haemorrhage did not recur, and necessitated no active therapy. Truelove, Horler, and Richards (1955) and Truelove and Richards (1956) reported excessive bleeding as a complication in their series of cases, but stated that it was infrequent. They also mentioned perirectal abscess, perforation, and dangerous tears of the rectal mucosa as possible complications; but Truelove (1960*b*) has not so far encountered these in his considerable series of biopsies. It seems reasonable to conclude that complications of this method of rectal biopsy are infrequent and not dangerous if the technique is properly and carefully carried out.

Results

1. *Histology.* The mildest and apparently the earliest change to be found was an excessive infiltration of the mucosa and lamina propria with either round cells or polymorphs. Eosinophils were not commonly present. The number of cells present bore some relation to the severity of the disease: the more severe symptoms and sigmoidoscopic changes were associated with a much greater infiltration. In more advanced or severe cases infiltration of the crypts with polymorphs was seen, and some crypt abscesses occurred, although the latter were not very common. Cases with gross sigmoidoscopic signs of activity showed evidence of actual erosion, ulceration, or even necrosis of the mucosa. This condition was usually associated with very extensive round-cell infiltration of the mucosa and submucosa. Cases of long-standing ulcerative colitis showed extensive round-cell infiltration of the mucosa, muscularis mucosae, and submucosa, often with some submucosal fibrosis. In healing or recently healed ulcerative colitis the specimens often showed evidence of flattening or simplification of the epithelial cells of the mucosa, although there might be no infiltration with polymorphs or lymphocytes.

In order to simplify the correlation of histological features with the clinical picture, the following numbers were allotted to signify various degrees of change in the specimens:

1 = Normal appearance.

2 = Some infiltration of the mucosa or lamina propria with either round cells or polymorphs.

3 = Much cellular infiltration of the mucosa, lamina propria, and submucosa.

4 = Presence of crypt abscesses, with much infiltration of all layers of the mucosa.

5 = Ulceration, erosion, or necrosis of the mucosa, with cellular infiltration of some or all of its layers.

2. *Chart of correlation in 126 cases.* The numbers used in the biopsy grading have already been explained. Those indicating the sigmoidoscopic findings have been used before (Matts, 1960*a*):

1 = Normal.

2 = Mild granularity of the mucosa, with mild contact bleeding.

3 = Marked granularity and oedema of the mucosa, contact bleeding, and spontaneous bleeding.

4 = Severe ulceration of mucosa with haemorrhage.

The grading of the state of the disease was simplified into three broad groups, 'active', 'semi-active', and 'quiescent'. In deciding in which of these groups each case should be classified, all the available information was considered. Particular attention was paid to the general feeling and symptoms of the patient, and the following features were recorded: the daily number of stools, whether they were formed or fluid, and the presence or absence of blood and mucus; the psychological condition, including the general feeling as regards well-being, and the presence or absence of depression; the occurrence of abdominal discomfort or pain, tenesmus, appetite, nausea, or vomiting; and especially the clinical course of the condition, whether static, getting better, or deteriorating. The findings on examination were also considered, including the sigmoidoscopic appearances, haemoglobin, and erythrocyte sedimentation rate. The assessment of the state of the disease was made before examining the biopsy specimen, in order to avoid any influence of the histological findings upon the grading. The Table summarizes the main features of each case; many lesser features cannot be presented in tabular form, and are omitted.

TABLE

Chart of Correlation in 126 Cases

Case number	*Sex*	*Age (years)*	*Haemoglobin (%)*	*Erythrocyte sedimentation rate* (mm./hour)*	*Stools daily*	*Blood*	*Mucus*	*Pain*	*Sigmoidoscopy grading*	*Rectal biopsy grading*	*Comment on disease*
1	F	50	95	36	8	+	+	+	4	4	Active
2	F	16	88	30	6	+	+	+	4	3	Active
3	F	41	90	24	4	+	+	—	3	2	Active
4	M	40	85	27	4	+	+	—	4	5	Active
5	F	41	80	30	3	+	+	+	4	5	Active
6	F	50	66	44	5	+	+	—	3	5	Active
7	F	49	69	40	3	+	—	—	2	3	Semi-active
8	M	21	78	13	3	+	+	—	3	4	Semi-active
9	M	60	94	10	2	—	+	—	2	3	Semi-active
10	F	55	92	12	4	+	+	—	3	3	Active
11	F	54	97	6	1	—	+	—	2	2	Quiescent
12	F	58	64	58	6	+	+	+	4	5	Active
13	F	54	72	10	2	—	+	—	2	2	Quiescent
14	M	22	91	9	4	+	+	+	3	5	Active
15	M	30	100	1	2	—	—	—	2	2	Quiescent
16	M	45	88	15	4	+	+	+	4	3	Active
17	F	70	86	25	2	—	—	—	2	1	Quiescent
18	F	19	67	53	10	+	+	—	3	5	Active

* Westergren method, uncorrected.

Case number	Sex	Age (years)	Haemoglobin (%)	Erythrocyte sedimentation rate* (mm./hour)	Stools daily	Blood	Mucus	Pain	Sigmoidoscopy grading	Rectal biopsy grading	Comment on disease
19	F	47	90	2	2	—	—	—	1	2	Quiescent
20	F	28	99	5	1	+	+	—	4	5	Semi-active
21	F	38	81	38	1	—	—	—	1	5	Quiescent
22	F	52	96	11	1	—	—	—	1	2	Quiescent
23	M	18	105	5	2	+	+	+	3	5	Active
24	M	24	96	11	3	+	+	+	4	5	Active
25	M	27	102	8	2	—	+	—	2	2	Quiescent
26	F	40	98	12	2–3	—	+	—	1–2	1	Quiescent
27	F	30	92	4	3	+	+	+	4	4	Active
28	M	50	86	40	4–5	+	+	+	4	5	Active
29	F	50	72	48	7	+	+	+	4	5	Active
30	F	56	86	33	2	—	+	—	2	3	Semi-active
31	M	41	94	2	1	—	+	—	1	1	Quiescent
32	F	43	62	23	3	+	+	+	3	3	Active
33	F	40	85	27	4	+	+	+	4	5	Active
34	M	52	104	2	2	—	+	—	2	2	Quiescent
35	F	40	90	12	3	—	+	—	2	3	Quiescent
36	F	44	96	3	4	+	+	—	1	1	Quiescent
37	F	70	86	18	3	+	+	+	4	5	Active
38	M	40	98	7	1	—	+	—	1	5	Semi-active
39	F	42	88	31	2	+	+	—	4	5	Active
40	F	38	91	20	1	—	+	—	1	3	Quiescent
41	F	54	96	26	5	+	+	—	4	5	Active
42	F	50	93	23	3	+	+	—	2	3	Semi-active
43	M	32	101	14	3	—	+	—	3	5	Active
44	M	35	99	14	4	+	+	+	4	4	Active
45	M	30	100	34	5	+	+	+	4	5	Active
46	M	53	82	46	12	+	+	+	4	5	Active
47	M	50	103	2	1	—	—	—	1	1	Quiescent
48	M	20	104	7	3	+	+	—	4	3	Active
49	F	19	87	5	7	—	+	+	3	3	Semi-active
50	F	56	89	25	3	+	+	—	4	4	Active
51	F	58	81	27	4	+	+	+	4	5	Active
52	M	18	89	24	3	+	+	—	3	4	Active
53	M	25	96	14	2	—	+	—	1	3	Quiescent
54	F	48	99	16	3	+	+	—	3	2	Semi-active
55	M	44	90	14	2	—	—	—	1	3	Quiescent
56	M	19	91	9	6	+	+	—	4	5	Active
57	F	54	90	12	6	+	+	+	3	4	Active
58	F	50	92	10	1	—	+	—	2	2	Quiescent
59	F	37	98	27	20	+	+	—	4	4	Active
60	F	40	91	28	1	—	—	—	1	3	Quiescent
61	F	48	60	48	6	+	+	+	4	5	Active
62	F	40	68	40	1	—	—	—	2	3	Quiescent
63	M	24	96	11	3	+	+	—	4	5	Active
64	M	30	102	8	1	—	—	—	2	3	Quiescent
65	F	46	66	44	2	+	+	+	3	5	Active
66	F	40	69	43	1	—	—	—	3	3	Semi-active
67	F	48	71	24	10	+	+	+	4	3	Active
68	F	50	80	21	5	+	+	—	3	3	Active
69	F	54	88	21	4	+	+	—	3	4	Active
70	F	52	85	20	4	+	+	+	3	4	Active
71	M	23	108	4	2	+	+	+	4	5	Active
72	M	20	96	11	2	+	+	—	4	5	Active
73	F	41	90	25	1	—	—	—	1	3	Quiescent

* Westergren method, uncorrected.

Case number	Sex	Age (years)	Haemoglobin (%)	Erythrocyte sedimentation rate* (mm./hour)	Stools daily	Blood	Mucus	Pain	Sigmoidoscopy grading	Rectal biopsy grading	Comment on disease
74	F	47	94	24	11	+	+	—	4	4	Active
75	F	50	92	9	1	—	—	—	2	2	Quiescent
76	F	54	90	11	6	+	+	+	3	4	Active
77	M	19	88	8	5	+	+	—	4	5	Active
78	M	40	90	11	2	—	—	—	1	2	Quiescent
79	F	47	99	14	3	±	—	—	2	2	Quiescent
80	M	30	98	13	2	—	—	—	1	3	Quiescent
81	M	18	91	23	3	+	+	—	3	4	Active
82	F	58	80	26	4	+	—	+	4	5	Active
83	F	53	90	23	3	+	+	—	4	4	Active
84	F	19	90	4	4	—	+	—	2	3	Quiescent
85	M	20	104	5	2	±	+	—	2	3	Quiescent
86	M	56	103	1	1	—	—	—	1	1	Quiescent
87	M	51	84	46	12	+	+	+	4	5	Active
88	M	29	101	29	6	+	+	+	4	5	Active
89	M	37	100	16	5	+	+	+	4	4	Active
90	M	30	90	14	3–4	—	+	+	3	5	Active
91	F	53	96	18	2–3	±	—	—	2	2	Quiescent
92	F	60	93	30	6	+	+	—	4	5	Active
93	F	37	95	18	1	—	—	—	1	3	Quiescent
94	M	43	99	8	1	—	+	—	1	4	Quiescent
95	F	66	88	19	3	+	+	+	4	5	Active
96	F	39	93	1	3–4	±	+	—	1	1	Quiescent
97	F	43	92	11	2	—	—	—	2	3	Quiescent
98	M	55	101	1	2	—	—	—	2	2	Quiescent
99	F	46	83	23	3–5	+	+	+	4	5	Active
100	F	41	62	29	5	+	+	+	3	3	Active
101	M	35	96	3	1	—	+	—	1	1	Quiescent
102	F	52	89	27	2–3	—	—	—	2	3	Quiescent
103	F	51	71	52	9	+	+	+	4	5	Active
104	M	56	88	42	5–7	+	+	+	4	5	Active
105	F	27	95	7	4	+	+	+	4	4	Active
106	F	38	97	11	3–4	—	—	—	1	1	Quiescent
107	M	30	105	3	2	—	—	—	2	2	Quiescent
108	M	18	97	4	5	+	+	+	3	5	Active
109	F	50	90	13	1	—	—	—	1	2	Quiescent
110	F	30	84	20	1	—	+	—	1	4	Quiescent
111	F	50	91	2	1–2	—	—	—	1	3	Quiescent
112	F	27	101	4	1–2	+	+	—	4	5	Semi-active
113	F	17	64	54	12	+	+	+	3	5	Active
114	M	23	93	8	4	+	+	+	3	5	Active
115	F	53	71	11	2–3	—	—	—	2	2	Quiescent
116	F	57	62	60	7–9	+	+	+	4	5	Active
117	F	51	94	7	1	—	+	—	2	2	Quiescent
118	M	61	92	12	2–3	—	+	+	2	3	Semi-active
119	M	23	77	15	3–4	+	—	+	3	4	Active
120	F	51	70	40	3	±	—	—	2	3	Quiescent
121	F	42	83	27	4	+	+	+	4	5	Active
122	F	55	93	9	4–5	+	+	+	3	3	Active
123	M	33	102	1	2	—	—	—	2	2	Quiescent
124	M	45	86	14	4	+	+	+	4	3	Active
125	F	72	88	29	3	—	—	—	2	1	Quiescent
126	M	40	86	30	4–5	+	+	—	4	5	Active

* Westergren method, uncorrected.

Summary of Correlation of Histological Changes against Severity of Disease

Biopsy grading	*State of disease*		
	Active	*Semi-active*	*Quiescent*
Number of cases showing:			
Gross changes (grades 4 and 5) . .	56	4	3
Moderate changes (grade 3) . . .	10	7	16
Mild changes (grade 2) . . .	1	1	18
Normal appearances (grade 1) . . .	0	0	10
Total number of cases—126 .	67	12	47
Percentage showing rectal biopsy changes . .	100%	100%	79%
Showing sigmoidoscopic changes:			
Number .	67	11	24
Percentage .	100%	92%	51%

Sigmoidoscopy and rectal biopsy both gave normal appearances in seven cases (all quiescent) (5·5 per cent. of all cases; 15 per cent. of quiescent cases).

Serious complications of rectal biopsy: 0.

Illustrative Case Histories

Certain of the case histories are of considerable interest in illustrating the value of rectal biopsy as an adjunct to other methods of diagnosis.

Case 19. A woman aged 47 was referred for diagnosis. She gave a vague history of occasional attacks of diarrhoea, possibly with traces of blood in the motions but none at the time of admission. The findings on sigmoidoscopy and on a barium enema were normal. Haemoglobin was 90 per cent., and the erythrocyte sedimentation rate 2 mm. in one hour. Rectal biopsy showed infiltration of both mucosa and lamina propria with round cells and a few polymorphs. A diagnosis of ulcerative colitis was made, and the patient was therefore followed up. Six months later she was admitted to the ward with a severe bloody diarrhoea which clinically, sigmoidoscopically, and later radiologically was confirmed as due to ulcerative colitis. It responded to therapy with prednisolone-21-phosphate enemata, and the patient has remained well since, apart from one slight relapse.

Case 21. A woman aged 38 was referred with a history of having had an attack of 'mucous colitis' 20 years ago. She had been fairly well since, but had recently been troubled with left-sided lower abdominal pain and loss of weight. Sigmoidoscopy and a barium enema gave normal results. Haemoglobin was 81 per cent., and the erythrocyte sedimentation rate 38 mm. in one hour. Rectal biopsy showed gross infiltration of all layers of the mucosa and submucosa with round cells. Some submucosal fibrosis was seen, and one small mucosal erosion was present. A diagnosis of ulcerative colitis was suspected from the history and raised erythrocyte sedimentation rate, but was made certain by the biopsy findings. A few weeks later, during a relapse of diarrhoea, the patient developed the sigmoidoscopic changes typical of ulcerative colitis.

She responded well to therapy with salazopyrin and local prednisolone-21-phosphate enemata.

Case 38. A man aged 40 was referred with a diagnosis of nervous diarrhoea. The history was of bouts of diarrhoea over the past nine months, usually associated with worry. Sigmoidoscopy and a barium enema gave normal results. Haemoglobin was 98 per cent., and the erythrocyte sedimentation rate 7 mm. in one hour. Rectal biopsy showed a small surface erosion in the mucosa, and gross infiltration of all layers of the mucosa with round cells and polymorphs. One crypt abscess was seen. A diagnosis of ulcerative colitis was made, and the patient was followed up. Two months later he developed a typical attack of ulcerative colitis with diarrhoea and bleeding, and characteristic sigmoidoscopic appearances of ulcerative colitis were then present. This attack cleared with local and systemic prednisolone, but he has had several minor recurrences of symptoms.

Case 53. A man aged 25 was referred with a vague history of having had an attack of diarrhoea seven years before, but remaining well since, apart from occasional episodes of diarrhoea when he was worried. The appearances on sigmoidoscopy and a barium enema were normal. Haemoglobin was 95 per cent., and the erythrocyte sedimentation rate 14 mm. in one hour. Rectal biopsy showed marked infiltration of the mucosa, lamina propria, and submucosa with round cells. A diagnosis of quiescent ulcerative colitis was made on the biopsy study. Eighteen months later the patient had a severe attack of ulcerative colitis, with bloody diarrhoea and collapse. On admission to hospital changes typical of ulcerative colitis were found both sigmoidoscopically and on barium-enema examination. He responded to transfusion and local and systemic prednisolone therapy.

Case 80. A man aged 30 was referred for diagnosis. He was said to have had a neurotic personality with marked hypochondriac tendencies. He complained of occasional passage of blood with the stools; there was no diarrhoea. The appearances on sigmoidoscopy and a barium enema were normal. Haemoglobin was 98 per cent., and the erythrocyte sedimentation rate 13 mm. in one hour. Rectal biopsy showed infiltration of all layers of the mucosa and submucosa with round cells. A diagnosis of ulcerative colitis was made. Eight months later the patient developed a typical attack, with confirmatory changes found on sigmoidoscopy and on a barium enema. He responded to therapy with salazopyrin.

Case 94. A man aged 43 was referred for diagnosis. Diarrhoea, of recent onset, was said to be associated with worry as to whether or not to emigrate to Canada. The appearances on sigmoidoscopy and a barium enema were normal. Haemoglobin was 99 per cent., and the erythrocyte sedimentation rate 8 mm. in one hour. Rectal biopsy showed infiltration of the mucosa and submucosa mainly with polymorphs, but with a few round cells. One crypt abscess was seen. A diagnosis of ulcerative colitis was made on the biopsy findings, and the patient was advised against emigration. Only two months later he developed a fairly severe attack of bloody diarrhoea, with sigmoidoscopic appearances typical of ulcerative colitis. His response to local prednisolone enemata was prompt and striking.

Case 111. A woman aged 50 was referred for diagnosis of vague left-sided abdominal pain associated with diarrhoea; there were up to three motions daily. Sigmoidoscopy and a barium enema gave normal results. Haemoglobin

was 91 per cent., and the erythrocyte sedimentation rate 2 mm. in one hour. Rectal biopsy showed infiltration of the mucosa with polymorphs; the lamina propria was infiltrated with round cells, and a few scattered round cells were seen in the submucosa. A diagnosis of ulcerative colitis was made on the biopsy findings, and the patient was followed up. Nine months later a very slight further episode of diarrhoea occurred, and another barium enema showed slight loss of haustrations in the descending colon, with an abnormal mucosal pattern.

In all the above cases the diagnosis was made on the rectal biopsy findings, and later confirmed by subsequent evidence. The histological findings have also been found to be of value in ruling out ulcerative colitis.

A woman aged 40 was referred for treatment of ulcerative colitis. She had a long history of attacks of diarrhoea associated with worry. Sigmoidoscopy showed an abnormally red rectal mucosa, with some obscuring of the veins on the surface. On a barium enema the radiologist pronounced the mucosal pattern as 'probably abnormal although not definitely so'. Haemoglobin was 95 per cent., and the erythrocyte sedimentation rate 3 mm. in one hour. Rectal biopsy gave a normal result. A diagnosis of nervous diarrhoea was made on this basis, and the patient was reassured. Follow-up has shown her to be perfectly well two years later.

A man aged 36, a tense and nervy subject, was referred as a proven case of ulcerative colitis on the basis of one abnormal sigmoidoscopy and dubious barium-enema findings. Sigmoidoscopy showed a rather reddened, but otherwise normal rectal mucosa. A barium enema showed an abnormal pattern of the mucosa of the sigmoid loop. Haemoglobin was 100 per cent., and the erythrocyte sedimentation rate 8 mm. in one hour. Rectal biopsy gave a normal result. The patient was reassured on the basis of the inconclusive history and normal biopsy findings. Subsequent follow-up and a further barium study showed him to be quite normal.

A woman aged 38 was referred for treatment of ulcerative colitis. She was thinking of giving up her work because she had been told she was suffering from this disease. Sigmoidoscopy gave a normal result. A barium enema showed some apparent mucosal changes in the descending colon, possibly attributable to ulcerative colitis. Haemoglobin was 78 per cent., with an iron-deficiency pattern; the erythrocyte sedimentation rate was 17 mm. in one hour. Rectal biopsy gave a normal result. The patient was reassured on the basis of normal biopsy findings and an inconclusive history. Eleven months later she was quite well; a further barium enema showed a completely normal appearance, and she had been able to continue her work as usual.

These three cases illustrate how normal biopsy findings, taken in conjunction with clinical assessment, can help to refute a previous diagnosis of ulcerative colitis. This conclusion is further supported by the fact that in the present series rectal biopsy gave a completely normal result in only 5·5 per cent. of cases of ulcerative colitis. It therefore seems reasonable to assume that normal findings are strong evidence against the disease. This is especially true of the active phase, since in the present series histological abnormalities have been detected in 100 per cent. of biopsies performed in cases showing the features of the active disease.

General Review of the Histology

Normal rectal mucosa has been adequately investigated in fresh biopsy specimens by Lumb and Protheroe (1955), who carried out 100 biopsies of the normal rectum. The mucosa of the large intestine does not form folds except in the rectum which, being devoid of villi, has a smooth surface. The crypts of Lieberkühn are straight tubules, and in the rectum attain a length up to 0·7 mm. These glands are very symmetrical in the normal rectal mucosa, and lie parallel, close to each other. The free surface between the gland openings is lined by simple columnar epithelium, with a thin striated border, and having occasional goblet cells. There are more goblet cells at the upper part of the crypts than at the bottom. The other cells at the bottom of the crypts, except for the occasional argentaffin cell, are epithelial cells, undifferentiated but often showing mitosis. These may develop into goblet cells (Florey, 1932). The lamina propria in the healthy rectum is scanty. It contains a stroma of argyrophilic fibres similar to that of lymphatic tissue, and becomes condensed to a reticular basement membrane at the epithelium-covered surface. Close to these fibres lie cells which have oval pale nuclei and can develop into macrophages. Among the meshes of this framework there are a few free cells, mostly lymphocytes and plasma cells; scattered lymphatic nodules also occur. These nodules are of various sizes, and may even traverse the fibres of the muscularis mucosae. The muscularis is well developed, and consists of circular and longitudinal strands. The submucosa presents no peculiarities; it consists of thick collagenous and elastic fibres with small arterioles, venules, and lymphatics. Most authors have commented on the similarity of appearance of specimens from healthy rectum (Lumb and Protheroe, 1955; Truelove, Horler, and Richards, 1955), and the present writer's experience confirms this view.

Acute ulcerative colitis. Specimens show a wide range of variation. In all cases there is infiltration of the mucosa with polymorphs and round cells, the polymorphs usually greatly predominating. The lamina propria is always involved in this infiltration, and shows excessive numbers of polymorphs and round cells. This cellular infiltration may extend further into the muscularis mucosae and the submucosa. Haemorrhages, usually small, may be seen in any of the layers of the mucosa. I have found no evidence of the frequent occurrence of excessive eosinophil infiltration reported by some authors (Bockus, 1944–6). The mucosa itself may show areas of shallow erosion, ulceration, or necrosis. In the specimens of the present series they never extended deeper than the muscularis mucosae. The ulcers are not usually large, probably because actual ulcers are not intentionally taken in biopsy specimens; and also because large deep ulcers are not seen in the rectum so commonly as in the colon, except in occasional patients who have been given long-term steroid therapy, in whom deep rectal ulcers may be seen surrounded by normal mucosa.

The question of crypt abscesses is of particular interest. They were found very commonly in the series of Lumb and Protheroe (1955), but less commonly by Truelove and his colleagues (1955, 1956). They occurred even less commonly

in the present series, and may be of less importance than has been suggested. Lumb and Protheroe (1955) felt that the crypt abscess was one of the primary lesions in ulcerative colitis. Truelove and Richards (1956) agreed as to the importance of these lesions, but were unable to decide whether their role was primary or secondary. The fact that they are not more frequently found in the active disease suggests that their role is secondary, and the constant presence of cellular infiltration in the mucosa and lamina propria, observed in the present series, suggests that this may be the site of the primary lesion.

In the specimens in which healing has occurred there is evidence of flattening and simplification of the cellular architecture of the mucosa, presumably as a result either of repeated regenerative healing of the mucosal cells, or of abnormal healing associated with the ulcerative colitis. This flattening is not observed in the healing of surgically inflicted wounds of the rectal mucosa (Lumb and Protheroe, 1955), and therefore must be associated in some way with the disease.

Subacute ulcerative colitis. The specimens may show small areas of surface necrosis, although there is no macroscopic evidence of ulceration. The cellular infiltration of the mucosa and lamina propria is less conspicuous, and the cells are more likely to be lymphocytes or plasma cells, although an excess of polymorphs is often present. The muscularis mucosae and submucosa may show excessive infiltration, or may be normal. Haemorrhages are infrequently seen in the specimens at this stage of the disease.

Quiescent ulcerative colitis. It is in this state that biopsy may be of the greatest value, because the sigmoidoscopic and other findings are sometimes equivocal or normal. The mucosa is usually intact, although not invariably so. Small erosions are very occasionally seen. The mucosal cells themselves may appear entirely normal, or may show some thinning, with a diminished number and irregular arrangement of crypts. The goblet cells are often excessive in number, and may account for the persistent passage of large quantities of mucus that sometimes occurs in this stage of the illness. The most consistently abnormal feature seen is the excessive infiltration of the lamina propria with round cells, which may also extend into the mucosa and submucosa. In long-standing cases the submucosa shows evidence of increased fibrous tissue, and sometimes dilated lymph channels are seen. The number of lymphoid follicles does not seem to increase in the quiescent stage but, when activity recommences, hypertrophy of the lymphoid follicles occurs and may account for the granular appearance seen on sigmoidoscopy.

Discussion

The study of freshly obtained specimens of rectal mucosa has provided much valuable information. It was first necessary to observe the histology of the normal rectum. This had already been adequately studied by Lumb and Protheroe (1955), and in the present instance their findings were confirmed by a few biopsies performed in normal cases. With knowledge of the normal

appearances it was easier to observe the abnormalities found in ulcerative colitis. It should be stated that no distinction in terminology has been made here between ulcerative colitis, proctitis, and proctosigmoiditis. This is because many authorities, who have carried out extensive investigations into these diseases, have found no evidence to justify such a distinction either histologically or clinically (Lumb and Protheroe, 1955; Truelove, 1959; Hightower, Broders, Haines, McKenney, and Sommer, 1958; Bockus, 1944–6; Bargen, 1935). This view is supported by the observations of most clinicians in whose experience the disease has commenced in the rectum and progressed, gradually or rapidly, to generalized ulcerative colitis. There seems every reason to suppose that the conditions referred to are all variants of ulcerative colitis.

The histological changes found in patients suffering from ulcerative colitis have already been described. They are clearly of a non-specific nature, and no absolutely positive diagnosis could be made on these changes alone. There are, however, in medicine very few diagnostic aids that are absolutely specific. Study has shown that the changes described are not present in the normal rectum, and further studies of patients suffering from nervous diarrhoea (Truelove and Richards, 1956; Lumb and Protheroe, 1955) have also shown histological normality. In the present investigation a few biopsies were carried out in patients suffering from nervous diarrhoea and patients with steatorrhoea, and no abnormal histological changes were detected in 10 specimens. Further, in five cases of Crohn's disease there was no detectable change in the rectal mucosa, a finding which was confirmed by Lumb (1958) in a series of biopsies. Histological changes similar to those seen in ulcerative colitis have been described as occurring in rectal biopsy specimens taken from cases of amoebic dysentery (Manson-Bahr and Muggleton, 1957). A differential point is that in these specimens there is very rarely the excess of polymorphs (Juniper, Steele, and Chester, 1958) often seen in acute ulcerative colitis, and amoebae are visible in 80 per cent. of the specimens. In acute bacterial dysentery the changes may be indistinguishable from ulcerative colitis. The fact that similar histological appearances occur in the dysenteries does not detract from the value of rectal biopsy in this country. Amoebic dysentery is uncommon, and bacillary dysentery is easily diagnosed by bacteriological and serological investigations. Where a diagnosis of amoebic dysentery is possible from the clinical history, examination of fresh stools and immediate examination of the biopsy specimens will usually enable the amoebae to be seen.

The clinical correlation of the biopsy results given in the Table shows a close relation between the severity of the histological picture and the sigmoidoscopic and blood changes. In some cases biopsy has afforded helpful diagnostic evidence where the other findings were normal or equivocal. In quiescent cases it appears that there is a greater chance of abnormal findings on biopsy than on sigmoidoscopy (79 per cent. and 51 per cent. respectively).

Rectal biopsy certainly seems to be of assistance in both the diagnosis and the exclusion of ulcerative colitis (see the illustrative case histories). It is not suggested as a routine measure in diagnosis, but is helpful in doubtful and

borderline cases. In such cases it should be regarded as additional evidence for the clinician to consider before making a decision which may affect the whole future of the patient. Fresh biopsy specimens are also of considerable value to those interested in the study of the natural processes of the disease, as one can learn from them the reactions of the different types of cell both to the disease and to different methods of therapy. In this connexion it is of interest that the biopsy specimens showed the most markedly abnormal changes in the superficial layers of the rectal mucosa, with a progressive diminution of activity as the deeper layers were reached. It follows that the local application of therapeutic solutions to the surface should have a chance of being effective. In practice this has been proved to be so (Matts, 1960*a*, *b*, 1961; Truelove, 1956, 1957, 1959, 1960*a*; Watkinson, 1958). Truelove (1956) has suggested that the progress of the disease towards healing can be assessed by studying biopsy specimens. The present writer's experience supports this view. Biopsy is particularly valuable when new methods of treatment are being tried, as the specimens can easily be submitted to an independent assessor for comment, making available a completely unbiased opinion separate from the clinical assessment. Bias on the part of the observer or the patient during the trial of any new therapy can thus be avoided, especially when a small series of cases is subjected to sequential analysis (Matts, 1960*a*, *b*).

Study of the biopsies in the present series shows no significant histological difference between ulcerative colitis, ulcerative proctitis, and non-specific proctosigmoiditis. This evidence favours the view, already stated, that these conditions are varieties of the same disease.

Analysis of the findings in this series casts some doubt on the role of the crypt abscess in the aetiology of the disease. If the part played by the crypt abscess is as significant as some authors have suggested (Lumb and Protheroe, 1955; Turell, 1959) one would expect to find it in all cases of active disease. If it is the precursor of the ulcer (Hightower, Broders, Haines, McKenney, and Sommer, 1958; Bargen, 1960) it should be present in all active cases in which ulceration is occurring. In the present series many cases have shown ulceration but no crypt abscesses on histological examination. This fact was also noted by Truelove and Richards (1956) and Truelove (1960*b*). These results suggest that one must search further for an aetiological agent in ulcerative colitis, and that the role of crypt abscesses is doubtful and possibly of little significance.

Rectal biopsy is both safe and simple, and is of value in three main ways: (1) as an aid to diagnosis in the borderline or obscure case; (2) to facilitate unbiased assessment of methods of therapy in ulcerative colitis; (3) as a research tool to aid the study of the natural processes of the disease, and to observe the breakdown and healing of the rectal mucosa in response to certain combinations of circumstances.

I should like to thank Dr. J. M. Naish, Dr. J. E. B. Pearson, Dr. F. Sutton, Dr. G. Mather, Dr. F. Page, Mr. T. J. Butler, Mr. C. Bartlett, Mr. W. M. Capper, and Mr. A. G. Macpherson, of the Bristol Royal, Frenchay, and Southmead

Hospitals, for allowing me to investigate their patients; and to thank the Pathology Departments at Frenchay and Southmead Hospitals, Bristol, and the Royal Hospital, Wolverhampton, for their co-operation and help.

The biopsy instrument and sigmoidoscope can be obtained from Vann Bros. Ltd., London.

Summary

The techniques of rectal biopsy have been reviewed, and a simple and safe method described and investigated.

The histological changes occurring in biopsy specimens of 126 cases of ulcerative colitis are described.

Correlation of these histological changes with the clinical picture has been carried out, and the results reviewed. Their significance in determining the aetiology of the disease is considered.

Histological changes in the rectal mucosa can be expected in over 90 per cent. of cases of ulcerative colitis.

The clinical value and use of rectal biopsy are described, and other local methods of diagnosis are briefly reviewed.

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FIG. 1. Rectal biopsy in quiescent disease with normal sigmoidoscopic appearances. The mucosa is histologically normal, but there is evidence of lymphoid hyperplasia in the submucosa, and a lymphoid follicle can be seen

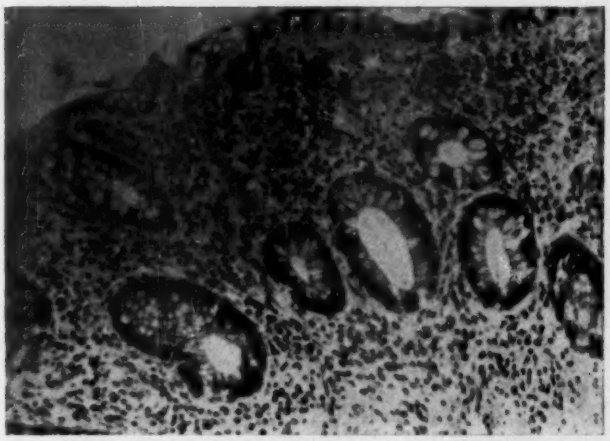

FIG. 2. Rectal biopsy in quiescent disease with slightly abnormal sigmoidoscopic appearances. The lamina propria is infiltrated with round cells, and there is evidence also of submucosal increase in round-cell activity

FIG. 3. Rectal biopsy in semi-active disease. There is marked infiltration of the mucosa and submucosa with polymorphs, lymphocytes, and plasma cells. Some mucosal exudate can also be seen

FIG. 4. Rectal biopsy in active disease. All layers of the mucosa and submucosa are heavily infiltrated with inflammatory cells. Lymphoid hyperplasia is also marked. The crypts contain exudate, and abscess formation may be occurring

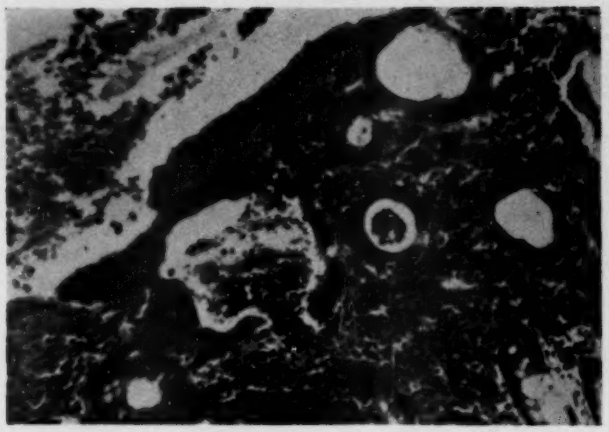

FIG. 5. Rectal biopsy in fulminant ulcerative colitis. Note the abnormal and oedematous appearance of the mucosal cells. The mucosa is heavily infiltrated with polymorphs in all areas, and shows breakdown in some places. Submucosal inflammation is also severe. Mucosal exudate is considerable, and crypt abscesses can be seen

FIG. 6. Rectal biopsy in very long-standing quiescent disease. Although the sigmoidoscopic appearances were normal, the specimen shows thinning and simplification of the mucosa and slight infiltration of the lamina propria with round cells

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1961

FIFTY-FIFTH ANNUAL GENERAL MEETING

THE FIFTY-FIFTH ANNUAL GENERAL MEETING was held in the H. H. Wills Physics Lecture Theatre, Bristol, on Friday and Saturday, April 14 and 15. The attendance book was signed by 237 members and 31 visitors.

The President, Dr. Donald Hunter, was in the Chair.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, was taken as read, confirmed, and signed. The Officers, Executive Committee, and Honorary, Senior, and Ordinary Members listed below were elected unanimously. The President explained that Sir Robert Aitken, Vice-Chancellor of Birmingham University, had previously been a Member of the Association but resigned when he went to New Zealand. The other five Honorary Members were all Fellows of the Royal Society and the Executive Committee of the Association felt that to elect them as Honorary Members was an appropriate way of paying tribute.

Executive Committee

President: Professor C. Bruce Perry.
President-Elect: Dr. Ernest Bulmer.
Hon. Treasurer: Dr. C. M. Fletcher.
Hon. Secretary: Dr. R. I. S. Bayliss.
Members for England and Wales:
Professor Melville Arnott.
Dr. R. Bodley Scott.
Dr. Charles Baker.
Dr. S. R. F. Whittaker.
Dr. C. A. Clarke.
Professor M. L. Rosenheim.
Members for Scotland:
Professor R. B. Hunter.
Professor K. W. Donald.
Dr. E. G. Oastler.
Members for Ireland:
Dr. S. Dundon.
Dr. M. I. Drury.
Dr. J. F. Pantridge.

Election of Honorary Members

Sir Robert Aitken.
Professor R. A. McCance.
Sir Harold Himsworth.
Professor J. McMichael.
Professor J. S. Mitchell.
Professor Sir George Pickering.

Election of Senior Members

Dr. E. A. Carmichael.
Dr. A. H. Douthwaite.
Dr. B. E. Schlesinger.
Dr. C. H. Whittle.

Election of Ordinary Members

Keith Percy Ball, M.D., M.R.C.P., Physician, Central Middlesex Hospital.
Edward James Moran Campbell, Ph.D., M.D., M.R.C.P., Assistant to the Professor of Medicine, Middlesex Hospital.

William Robert Macfarlane Drew, C.B.E., M.D., F.R.C.P., Director of Studies, Royal Army Medical College.

Thomas Terence Fulton, M.D., M.R.C.P., Physician, Belfast Hospital Group.

Michael Jefferson, M.D., F.R.C.P., Consultant Neurologist, United Birmingham Hospitals.

Donald Longson, M.B., M.R.C.P., Physician, United Manchester Hospitals.

Michael Bernard Matthews, M.D., M.R.C.P., Physician, Western General Hospital, Edinburgh.

Richard Bonar McConnell, M.D., M.R.C.P., Physician, United Liverpool Hospitals.

John Patrick David Mounsey, M.D., M.R.C.P., Lecturer in Medicine, Postgraduate Medical School, London.

Borje Edgar Christopher Nordin, Ph.D., M.D., M.R.C.P., Senior Lecturer in Medicine, University of Glasgow.

Alan Ernest Alfred Read, M.D., M.R.C.P., Lecturer in Medicine, University of Bristol.

George Oglethorpe Richardson, M.D., F.R.C.P., Physician, General Hospital, Newcastle.

Eric John Ross, Ph.D., M.D., M.R.C.P., Senior Lecturer, University College Hospital Medical School.

David Somerset Short, Ph.D., M.D., M.R.C.P., Physician, Aberdeen Royal Infirmary.

Walter Somerville, M.D., F.R.C.P., Physician, Middlesex Hospital.

Robert Elsworth Steen, M.D., F.R.C.P.I., Professor of Paediatrics, University of Dublin.

Oswald Arthur Savage, O.B.E., F.R.C.P., Physician, West London Hospital.

The Treasurer presented the accounts, and said that up to 1951 the *Journal* had cost Members 25*s*., which with a subscription of 2 guineas left 17*s*. for administration. In 1959 the price of the *Journal* had risen to 42*s*. 6*d*. and the subscription to £3, so that there was still 17*s*. 6*d*. available for administration. Even so it had been necessary to impose a registration fee at the Annual General Meetings because of their increased cost. The increase in size of the *Quarterly Journal* would now mean that it would cost 50*s*. to Members, and although with the reinvestment of the Society's capital the Association was showing an excess of income over expenditure of some £200 per annum, the Committee had thought it better to provide against further increases by raising the annual subscription. This would mean that the registration fee for future Annual General Meetings could be abolished. The Treasurer said that if Members felt so disposed he thought the increased subscription could safely be deferred for a year or two to see whether the Association would remain solvent.

The Meeting agreed to increase the annual subscription, and accordingly Rule 19 was amended to read: 'The subscription of Ordinary Members shall be £4 a year, and of Senior Members £2. 10*s*. a year, which shall entitle them to receive a copy of each issue of the *Quarterly Journal of Medicine* for the corresponding year.'

Place of Future Meetings. In 1962 the Annual General Meeting will be held in Birmingham on Friday and Saturday, May 4 and 5. Professor I. W. G. Hill reaffirmed the invitation for the meeting in 1963 to be held in Dundee.

The newly elected President, Professor C. Bruce Perry, then took the Chair, and paid tribute to Dr. Donald Hunter.

SCIENTIFIC BUSINESS

Friday Morning, April 14

1. An account of *Progressive 'Juvenile' Cirrhosis* was given by PROFESSOR C. V. HARRISON (introduced), DR. A. E. A. READ, and PROFESSOR SHEILA SHERLOCK. Fifty-three patients had been studied; 38 of them were female, and most less than 40 years old. A history strongly suggestive of a previous attack of viral hepatitis was obtained in 17. In many patients the jaundice was of long duration with remissions and exacerbations, and in some there was a marked tendency to develop 'multiple organ' involvement. Thus arthralgia, involvement of the serous membranes, and various endocrine abnormalities were not uncommon; 10 patients had a positive L.E. cell test. The histological features had been studied by needle biopsy and *post mortem*. In the early phases there was evidence of liver-cell damage with portal cell infiltration and a variable degree of hepatic fibrosis. Subsequent progression led to the appearance of post-necrotic cirrhosis. Serial biopsies obtained from patients treated with corticosteriods had shown variable changes, with occasional improvement in liver-cell morphology, but there was no evidence that such treatment prevented the development of cirrhosis, although in about half there was biochemical evidence of improvement in liver-cell function (fall in serum bilirubin, globulin, and transaminase

values, and rise in serum albumin), and relapse after stopping treatment was not uncommon. The prognosis was variable, but about one-third of the patients had died, usually within four or five years of the commencement of the disease. The hazards of treatment with corticosteroids were discussed, and the relation of this syndrome to acute viral hepatitis and the possible role of auto-immune factors in its progressive course were considered.

In reply to PROFESSOR A. MONCRIEFF, who asked if any of the patients had had babies while they had the disease, and if so whether the babies were jaundiced or showed evidence of liver disease, DR. READ said that four women had become pregnant while jaundiced. In three the pregnancy had been terminated elsewhere, and the fourth patient, who also had mitral stenosis, had a premature labour, with delivery of a still-born child without evident liver disease.

DR. W. T. COOKE commented that it was his impression that male patients with this disorder did not respond as well as females, especially with regard to the fall in globulin, on treatment with corticosteroids.

DR. R. W. LUXTON showed slides of a woman with Hashimoto's disease and hepatic cirrhosis. In 1947, when the patient was aged 33 years, Hashimoto's disease was treated by radiotherapy, and at that time the liver was found to be enlarged. Symptoms of progressive hepatic cirrhosis, with jaundice, ascites, and hypercholesterolaemia, arose subsequently, and the patient died in hepatic failure in 1957. Histologically the liver showed areas of regeneration hyperplasia separated by wide bands of connective tissue infiltrated by plasma cells and lymphocytes. The histology so closely resembled that of Hashimoto goitre that the speaker described it as 'Hashimotosis of the liver'. Furthermore, the speaker had seen nephropathies in Hashimoto's disease, and considered that multiple auto-immune disorders tend to occur in the same patient.

DR. A. R. KELSALL said that a marked eosinophilia had been a striking feature in the early stages of an otherwise typical case, and the eosinophil count fell to normal when corticosteroid treatment was started. DR. READ replied that an eosinophilia had not been a feature of any of his cases.

DR. J. M. NAISH said he was puzzled as to when the disease began. Certainly it was long before jaundice developed and before there was any cirrhosis of the liver. In support of this he showed a photomicrograph of a liver biopsy specimen from a girl of 16, who had typical lupoid hepatitis with striae, acne, and L.E. cells in the peripheral blood. There was no evidence of cirrhosis, and only minimal portal-tract infiltration with round cells. A further liver biopsy 18 months later, after a relapse following withdrawal of steroid therapy, showed more liver-cell infiltration, but still no cirrhosis. It was doubtful whether this disease should be called 'progressive juvenile cirrhosis' when cirrhosis was only one end-result of the disease process, and he preferred 'lupoid' or 'autoclastic hepatitis'.

DR. J. W. PAULLEY asked if either of the two patients who also had ulcerative colitis developed this before or after hepatic cirrhosis. Willcox and Isselbacher had recently described cases where the hepatitis appeared to antedate the colitis. He used the word 'appeared' with intent, because the date of onset of colitis was difficult to fix and often rectal bleeding was passed off for years as piles. The literature, and his own observations, suggested that an abnormal bacterial intestinal flora led to infection of portal blood and bile, a pericholangitis, and thus to a proportion of the cases of juvenile cirrhosis. In reply DR. READ said that in one patient the colitis apparently antedated the hepatic disorder, and in the other the colitis began after corticosteroids for the liver disease had been started.

DR. W. G. OAKLEY said that the only case of juvenile cirrhosis in a diabetic of which he had had personal experience was insulin-resistant. He asked whether the other diabetics with juvenile cirrhosis reported showed any evidence of resistance to insulin, and what effect steroid therapy had had on their insulin requirements. DR. READ said there had been four patients with diabetes, and in three of them this had started before the hepatic disease became manifest. All patients, including one with an insulin-binding factor in the serum, had increased insulin requirements as a result of steroid therapy.

DR. J. F. STOKES said that the evidence for this type of disease being due to an auto-immune process seemed very strong. He commented on the amenorrhoea, which was difficult to explain except on the basis of its occurrence in any ill patients. DR. READ replied that the amenorrhoea was probably a non-specific feature related to the activity of the disease and could be correlated with the degree of hyperbilirubinaemia and elevation of the transaminases.

DR. G. WATKINSON asked about the duration of corticosteroid therapy and the indications for stopping it. DR. READ explained that it was difficult to decide for how long steroids should be given. The patients responded to small doses, and nine to twelve months' treatment, depending on the clinical and biochemical response, seemed necessary. In some patients relapse on stopping treatment required two or more periods of treatment.

In reply to PROFESSOR STUART-HARRIS, DR. READ said that although a previous history of infective hepatitis was common, none of his patients had apparently suffered from homologous serum jaundice.

2. DR. B. P. ROBINSON (introduced), PROFESSOR A. G. DORNHORST, and DR. A. LEATHAM described a technique for making *Carotid Pulse Recordings by an External Method*. DR. ROBINSON said that peripheral effects caused considerable change in the pulse wave during transmission, and it was desirable to use the central pulse as a guide to cardiac abnormalities. Direct puncture of the aorta or carotid artery being unsuitable for routine use, an external method of recording the carotid pulse had been devised. An air-filled cuff around the neck was used, and gave satisfactory and reproducible results. In the absence of hypertension, the volume pulse so obtained had been found to correlate well throughout systole with the simultaneously recorded pressure pulse. The normal carotid pulse showed a sharp early rise followed by a plateau which might rise or fall slowly. The pulse had been studied in 30 patients with proved valvular aortic stenosis. An initial short rapid rise was usually seen, terminating at an anacrotic shoulder from which there was a slow further rise, interrupted by coarse vibrations and leading to a late peak. Variations, however, did occur. The ejection time (onset to incisura) was more often prolonged than the upstroke time (onset to highest point) but in seven patients neither of these measurements were abnormal. Each of these, however, had shown typical changes in the shape of the pulse, and diagnostic abnormalities were thus present in every case.

When significant aortic regurgitation accompanied stenosis the pulse had shown a high and well-marked anacrotic notch. As a result of transmission changes this could give rise to a bifericns brachial pulse.

DR. D. VEREL asked what effect changes in posture had had on the tracing obtained, because elevation of a limb induced a marked increase in pulsation associated with a decrease in flow and in blood-pressure. In reply, DR. ROBINSON said that the recordings had been made with the patients at an angle of 60° to eliminate venous pulsations. In answer to DR. W. SOMERVILLE he said that the thickness of the neck did not influence the carotid pulse tracing, and in reply to DR. W. B. MATTHEWS he said that no observations had been made on the effect of occlusive disease of the carotid itself on the form of the recorded pulse.

3. DR. D. A. J. TYRRELL (introduced by PROFESSOR STUART-HARRIS) recounted some *Studies of Cold Viruses*. He said that clinical observations had shown that colds were apparently due to infectious agents, and that most people suffered repeated attacks. Work at the Common Cold Research Unit had confirmed that the infectious agent was a virus, but about two-thirds of volunteers challenged with a variety of strains seemed to be resistant to infection. A method for cultivating in tissue culture certain viruses causing common colds had been developed, and it had been found necessary to use a lower pH (6·8 to 7·4) and a lower temperature (33° C) than were usually employed in tissue culture work. If cultures were kept in unfavourable conditions, e.g. stationary (poorly oxygenated), or at unsuitable pH or temperature, then foci of degeneration (microplaques) induced by the virus failed to develop. Microplaques had also been inhibited by treating the virus with antiviral serum or by treating the cells with interferon. Some of these *in vitro* mechanisms might account for the resistance of volunteers to experimental colds. The pH and temperature of the anterior nasal mucosa had been measured; they averaged 7·3 and 31·4° C, and were usually in the optimal range for *in vitro* cultivation of the virus. The nasal mucosa was obviously well oxygenated. Human serum, however, apparently contained antibodies against at least some cold viruses, and there were marked antibody responses to natural and experimental infection. Sixteen of 25 volunteers with little or no antibody in the serum ($K < 0{\cdot}22$) were susceptible to experimental infection with H. G. P. or B632 viruses, but only four out of 44 with higher levels of antibody. The viruses seemed to multiply in the nose rather than in the conjunctiva or gut. Nasal secretions from eight of 11 volunteers contained an inhibitory substance acting against B632 virus. The titres were not clearly correlated with serum antibody levels, but two of the three without inhibitor in the nose had no antibody in the serum, and there was no volunteer with inhibitor in the nose without antibody in the serum. The presence of specific antibodies apparently explained the resistance of most subjects to experimental inoculation of cold virus. Seven or more serotypes of virus had so far been distinguished, and the number of different antigenic types probably accounted for the high frequency of clinical colds, especially in younger persons. The temperature of the nose rose 1° C or more during six of 10 colds, and fell during convalescence, but there was no increase of inhibitor in nasal secretion in the few cases that had been tested. It is reported in the literature that nasal secretion early in a cold is alkaline, and this would tend to inhibit

growth of these viruses. The nasal pH in experimental colds at Salisbury had not yet been measured. The factors leading to the disappearance of virus from the nose obviously required further study.

PROFESSOR SIR ROBERT PLATT said he was sure DR. TYRRELL would know of the work of Hope Simpson which seemed to show a very close correlation between the incidence of colds and climatic conditions, suggesting that the virus might be present in the upper respiratory tract and activated by environmental changes. In reply, DR. TYRRELL said that although he accepted the data that the frequency of colds increased to a degree closely related to the mean outdoor temperature, this did not mean that virus was being carried by many people and brought into prominence when the weather changed. Silent infections were uncommon in experimentally inoculated subjects, and virus had not been isolated from people without colds. Colds seemed to behave as a short-term specific infection, and it was possible that transfer of virus from person to person might be affected by environment. Preliminary work by Buckland, however, had shown that cold viruses were more readily inactivated in air of low relative humidity (such as would be found indoors in winter) than in air of high relative humidity. The matter needed much more investigation, and it should be possible to bring it in line with the facts on colds in volunteers. Perhaps it was like a fire in which a smoulder might be transformed into a blaze by a relatively small change in the conditions.

In reply to PROFESSOR A. MONCRIEFF, who asked if there was any waxing or waning of immunity in the inoculated subjects, DR. TYRRELL said that antibody to colds seemed to persist for years. In answer to PROFESSOR A. V. NEALE he said that antibody had not been measured in umbilical cord blood at birth, but he presumed it would be present in fairly high titres as in the mothers.

Replying to DR. C. M. FLETCHER, who asked whether the nasal temperature rose in a hot room, and whether this might reduce susceptibility to colds, he said that in one short-term series of observations it was found difficult to raise the temperature of the nasal mucosa except by exposing the subject to conditions like those of the humid tropics. In answer to DR. J. F. STOKES he said the normal temperature of the anterior nasal mucosa averaged 31° C or more. DR. K. D. KEELE asked whether—since DR. TYRRELL had suggested that the termination of a cold was due to a change in the temperature of the nasal mucous membrane—the effects of whisky and lemon on the mucous membrane had been investigated, but DR. TYRRELL replied that no such observations had been made.

4. DR. C. J. SCHWARTZ and DR. J. R. A. MITCHELL (introduced by PROFESSOR SIR GEORGE PICKERING) reported on *Atheroma of the Carotid and Vertebral Arterial Systems* as found in a random necropsy survey of 93 patients aged 35 and over, the vessels being dissected out from the arch of the aorta to the circle of Willis. DR. MITCHELL stressed the patchy nature of the disease, and noted that whereas the carotid sinuses were often severely affected, the segment immediately beyond the sinus was remarkable for its freedom from disease. Haemodynamic factors seemed to play an important part in the localization of lesions, and arteries which came off their parent trunk at right angles—the vessels springing from the aortic arch, and the vertebral arteries arising from the subclavians—had a high incidence of proximal stenosis, whereas the right common carotid, a straight continuation of the innominate, seldom had proximal lesions. He emphasized that the lesions were commonly multiple, and said that in their series, and in a larger group of patients subsequently examined, if one sinus were severely narrowed, there was only a 19 per cent. chance that the opposite sinus would be normal, whereas a patient with a normal sinus on one side had an 80 per cent. chance that the other sinus would be similarly normal. He said that in this random sample there was a very high prevalence of severe carotid and vertebral stenosis (present in one man in four in the vertebrals, and one man in seven in the carotids), and showed that there was little difference between the neck arteries in these unselected patients and 83 patients with strokes described by Hutchinson and Yates (1957). He discussed in more detail 27 patients with strokes who had been studied as part of the random series, and said that although there was a strong correlation between neck artery occlusion and cerebral infarction, the relationship for simple narrowing seemed less clear cut. The prevalence of strokes was dependent on age even in patients with normal neck arteries, and, as the severity of atheroma was also dependent on age, a false correlation between neck artery disease and strokes might be found even though they were not causally connected.

PROFESSOR SIR ROBERT PLATT asked, in view of the recent paper by Dickinson and Thomson, whether DR. MITCHELL had correlated the blood-pressure of the patients studied with the degree of atheroma present. Had he any comments on Dickinson and Thomson's findings which seemed to relate blood-pressure to the capacity of the carotid and vertebral arteries? In reply, DR. MITCHELL said that Dickinson and Thomson had investigated

the relationship between blood-pressure in life and the flow rate through perfused arteries in the cadaver. They had found a stronger correlation for the vertebral artery than for the carotid, and virtually none for the femoral, and reasoned that if raised blood-pressure simply increased atheroma deposition in the arteries, all three vessels should show the same degree of correlation. The arteries, however, were of very different size, as was clearly shown in their paper by the size of cannulae used. If one assumed that a given thickness of atheroma resulted from a given elevation of arterial pressure, it would affect the calibre of the narrow vertebral artery more than the wider carotid and the still wider femoral. Far from showing a special relationship between vertebral narrowing and hypertension, DR. MITCHELL maintained that this study had only shown that vessels of differing size behaved differently. In his own series, which being unselected contained patients from the accident services and surgical wards, there had been insufficient data on the blood-pressure to permit pressure and arterial stenosis to be correlated.

DR. J. C. GILSON asked whether an analysis had been made separating the accident cases from the rest, and if so whether there was any difference between the two groups. The findings based on accident cases were more likely to be representative of the general population than those derived from deaths of all causes. DR. MITCHELL replied that accident cases were highly selected, there being usually more men than women, and many were young. In reply to PROFESSOR W. J. H. BUTTERFIELD he said that there was no reference in the hospital notes to any carotid bruits being heard. DR. J. W. PAULLEY asked whether any signs of inflammation of the external wall had been seen in cases with recent thrombosis, but DR. MITCHELL assured him that no inflammatory changes had been seen in any of the thrombosed arteries. In answer to DR. R. L. RICHARDS, who asked whether in the cases with a history of a stroke examination of the brain showed lesions, and whether these changes could be correlated with the pathology in the carotid and vertebral arteries, DR. MITCHELL said that the strokes were due to cerebral infarction. DR. J. B. STANTON said that there were occasional instances of occlusion of both carotid and both vertebral arteries not being fatal. He asked if in DR. MITCHELL's experience thrombosis of all four vessels was invariably fatal. DR. MITCHELL replied that in his series no patient had occlusion of more than two vessels. In answer to DR. E. J. M. CAMPBELL, DR. MITCHELL said there was a good correlation between the site of the thrombosis in the neck and the area of cerebral infarction.

5. DR. R. FINN (introduced by DR. C. A. CLARKE) described some experimental work which might lead to *Protection against Erythroblastosis*. Based on the technique of Kleihauer (1957) it had been found possible, using a citric-phosphate buffer (pH 3·5 at 37° C for 90 seconds) to elute adult haemoglobin from adult red cells whilst leaving behind foetal haemoglobin in foetal red cells. By this procedure it had proved possible to investigate the occurrence and volume of transplacental haemorrhage. For example, in the mother of an infant born with a haemoglobin level of 73 per cent. a large number of foetal red cells were found in the maternal circulation. The infant was S+ and the mother S−, and the diagnosis was confirmed by demonstrating small agglutinates of S+ cells in the mother's blood after incubation with anti-S serum at 4° C. Small transplacental haemorrhages associated with delivery occurred in about 11 per cent. of mothers. The bleeding was usually about 1 ml., but occasional larger bleeding of 5 ml. or more occurred. The occurrence of transplacental haemorrhage had been correlated with the development of antibodies in the puerperium, and sensitization (development of anti-D antibodies) demonstrated in two out of three women with large transplacental haemorrhages (5 ml. or more), whereas only one questionable case was detected in 75 women (with Rh-positive children) in whom no transplacental haemorrhage had been demonstrated. It was therefore concluded that erythroblastosis was uncommon because transplacental haemorrhage occurred in only a small percentage of women. The antigenic stimulus seemed to occur in most cases during labour, because the incidence of transplacental haemorrhage at this time was high enough to account for the natural incidence of the disease. DR. FINN suggested that it might be possible to destroy any foetal red cells present in the maternal circulation after delivery, and thus prevent Rh sensitization and the occurrence of haemolytic disease in a subsequent pregnancy. In a pilot experiment 5 ml. of Rhesus-positive blood tagged with ^{51}Cr had been injected into six Rh-negative male volunteers. Thirty minutes later three of the volunteers had been given 10 ml. of anti-D serum; this caused coating and destruction of the Rhesus donor cells. These results suggested that erythroblastosis could be prevented.

PROFESSOR A. MONCRIEFF asked whether it was proposed to give 'blind' injections of anti-D serum to mothers immediately after delivery of their first baby when the mother was Rh− and the father Rh+. He also asked about the supply of anti-D serum. DR. T. H. BOON asked whether it was supposed that progressive increase of antibody titre

in successive pregnancies in sensitized mothers was due to transfer of considerable amounts of foetal blood to the maternal circulation in each pregnancy. DR. J. B. L. HOWELL pointed out that if the calculation of the volume of foetal blood added to the maternal circulation was based solely on its dilution, this might represent a considerable underestimation. The numbers of foetal cells present would be the balance between their destruction and their addition to the circulation, and might represent a larger infusion of foetal blood than had been calculated. PROFESSOR A. V. NEALE said that although it was probably true that the greatest transfer of foetal blood to the maternal circulation occurred during labour, there was evidence that minor passage might be detected during pregnancy, and possibly at times of threatened or actual abortion, which would therefore call for careful examination of the maternal blood at intervals. He also inquired whether, even if all the D cells were haemolysed by anti-D serum, the D antigen would be *ipso facto* destroyed. There was evidence that the antigen would persist after haemolysis of the cells.

DR. F. J. W. MILLER asked whether any relationship had been established between large transfers of blood from infant to mother and clinical events in pregnancy or delivery. Work in Newcastle by Drs. E. G. Knox and W. Walker indicated that there was a correlation between abnormal pregnancy, especially toxaemia, and the development of sensitivity. DR. TYRRELL asked whether there was experimental evidence that Rhesus antigen when combined with antibody no longer stimulated antibody production in man. In other systems antigen–antibody complexes had been used for immunization.

In reply, DR. FINN said that although it was well known that the R_2 (cDE) antigen was more likely to stimulate antibody production than the R_1 (CDe) antigen, it was unlikely that the ability of the mothers to produce antibodies could be the sole determinant of Rh iso-immunization, because experimental immunization following injections of Rh-positive blood led to antibody production in over 50 per cent. of subjects, a figure far in excess of the 5 per cent. incidence of pregnancy iso-immunization. It was therefore probable that the low incidence of the disease was due primarily to the fact that only a small percentage of foetuses acted as immunizing stimuli; in other words, transplacental haemorrhage was the principal determinant of immunization. There was as yet no evidence as to whether transplacental haemorrhage was a random phenomenon or secondary to other pathological conditions such as maternal toxaemia. There was some evidence that toxaemia predisposed to Rh sensitization, and hence a relationship with maternal toxaemia was probable. Rh iso-immunization was extremely uncommon in ABO heterospecific pregnancies, and this was due to the rapid destruction of ABO-incompatible foetal red cells on entering the maternal circulation. It was therefore probable that destruction of foetal cells by other means (e.g. the injection of anti-D serum) would be equally effective in preventing sensitization.

In any clinical trial designed to test this hypothesis, women would be screened for foetal cells after delivery, and anti-D would be given only to those with proven transplacental haemorrhage. As this would apply to only a small percentage of Rh-negative mothers, there would be no problem concerning the supply of anti-D serum.

6. PROFESSOR C. BRUCE PERRY spoke on the *History of Bristol Medical School*. He said that medical education in Bristol probably started with the Guild of Barber Surgeons. The Infirmary was founded very near the present site in 1737, and pupils were attached to the Surgeons and to the Apothecary from the earliest days, but physicians were not allowed to have pupils until 1832. In the 18th century there were many schools of Anatomy and of Medicine and Surgery, but the best of these combined in 1833 to found the Bristol Medical School. New infirmary buildings were completed in 1811, and these formed the nucleus of the present medical wing. The last extension was the King Edward VII memorial building, opened in 1912, and now housing the surgical departments. A rival institution, the General Hospital, was opened in 1832. The two hospitals remained independent and largely separate teaching units until 1940, when they amalgamated as the Bristol Royal Hospital, to which other smaller hospitals were added in 1948 to form the United Bristol Hospitals. In 1879 the Medical School was affiliated to the new University College, and in 1909 became the Faculty of Medicine of the University of Bristol, which then received its charter. A notable member of the staff in the 18th century was Edward Lyne, whose favourite prescription for dropsy was 'Bristol Milk'. Two famous physicians in the 19th century were William Budd, epidemiologist, and John Beddoe, anthropologist. W. G. Grace enrolled as a medical student in 1869. Distinguished physicians in this century have been Carey Coombs, George Parker (President of the Association in 1924) and J. A. Nixon (President in 1938). A new Medical School building should be completed by 1965, and plans were maturing for new hospital buildings.

After lunch in the Reception Room of the University's main building, preceded by sherry kindly provided by the Board of Governors of the United Bristol Hospitals, the

afternoon was devoted to the study of a large number of excellent scientific demonstrations in the Queen's Building, the new Engineering School of the University.

Annual Dinner

The Annual Dinner was held in the Council House of the Municipal Buildings, after a sherry party given generously by the Bristol members. The President, Professor C. Bruce Perry, was in the Chair. He proposed the Royal Toast, and drank the health of the Association and its guests. The Vice-Chancellor of Bristol University, Sir Philip Morris, replied. The toast of the President was proposed by Professor Sir Robert Platt.

Saturday Morning, April 15

7. Drs. H. J. Goldsmith, J. H. Peters, and M. Zomeno (introduced by Dr. E. W. Skipper) described the *Evolution of Renal Disease in Scleroderma*. Twenty-six patients had been divided on clinical grounds into three groups, and their renal histology studied at autopsy or by needle biopsy. In the acute group the illness had run a rapidly progressive course, characterized by marked constitutional disturbance, rapid and extensive evolution of cutaneous changes, and weight loss, and often by fever, polyarthritis, and exertional dyspnoea. These patients had often shared certain clinical features with cases of diffuse lupus erythematosus, dermatomyositis, or polyarteritis, but none had shown the L.E. phenomenon in the peripheral blood. Their mortality rate had been high, death usually having resulted from cardiac or renal failure with hypertension. Patients in the chronic group had been ill for some years with classical, slowly progressive scleroderma. They had tended to remain normotensive, with adequate renal function. The subacute group had been intermediate in type, resembling the acute more than the chronic group. The characteristic lesion of the sclerodermatous kidney was a striking intimal thickening of the smaller renal arteries. This lesion had been observed at an early clinical stage of the disease, several years before death. Two distinct patterns of intimal change had been noted. The first, a 'mucoid' swelling of the intima, was present in pure form only in the acute group, and was associated with death from rapidly progressive hypertension with cardiac or renal failure; the second, a 'hyperelastotic' intimal thickening, was present in pure form only in the chronic group. This lesion, though present from an early stage, increased in severity with the duration of the disease. Biopsies showing virtually occluded interlobular arteries had been obtained from patients with normal urine, blood urea, and blood-pressure. Hypertrophy of the juxta-glomerular apparatus had paralleled the degree of arterial narrowing, possibly owing to low pulse-pressure in the afferent arterioles.

Professor D. A. K. Black said that lesions in the interlobar arteries, similar to those described, had been seen in patients who presented with malignant hypertension, were treated with hypotensive drugs, and died some years later. Had any of Dr. Goldsmith's patients received hypotensive agents? Dr. H. Dimsdale asked what abnormalities of the fundi had been observed in the rapidly progressive and chronic forms.

In reply, Dr. Goldsmith said that the blood-pressure had remained normal in most cases of chronic scleroderma, and hypotensive drugs had not been used. No retinal lesions had been observed in patients with the chronic disease, but a few retinal haemorrhages were seen in patients of the acute and subacute group who died of hypertension and acute renal failure.

8. The *Indications for Closure of Ventricular Septal Defects* were described by Dr. J. F. Goodwin and Drs. A. Hollman, W. P. Cleland, and H. H. Bentall (introduced). Ninety-five patients had been operated upon with the use of a cardiopulmonary bypass and the Melrose-N.E.P. pump oxygenator. Most were children between the ages of six and 10 years. Many had been physically active, some had few symptoms, but a number were physically underdeveloped and prone to frequent respiratory infections. Indications for operation had been a shunt large enough to produce a ratio of pulmonary to systemic blood-flow of 1·5 to 1 or more, and pulmonary vascular disease. Patients with a right-to-left shunt were excluded. Of the 95 patients, 82 had been greatly benefited, 13 died, and 18 had residual shunts, which were minimal in 11. The major hazards of the operation were pulmonary vascular disease, associated cardiac lesions, complete heart-block arising during the operation, and acute reopening of the defect in the immediate post-operative period. Pulmonary vascular disease was of major importance in determining the risks of the operation and in predicting the result. There was no close relationship between the size of the defect and the pulmonary vascular resistance, but when the defect was 1 to 2 sq. cm. per sq. metre of surface area or less, the resistance was, with one exception, normal. Defects up to 3 sq. cm. were often associated with a normal resistance. A low

resistance with medium-sized defects was often due to pulmonary stenosis or infundibular hypertrophy. The mortality rate was significantly higher in patients with a pulmonary arteriolar resistance of 8 units or more, as was the incidence of complete heart-block and of residual shunts following the operation. The residual pulmonary artery pressure immediately after closure was an important prognostic guide, patients whose pulmonary artery pressure was still more than half the systemic pressure having a higher mortality rate and a poorer final result. The importance of a high pulmonary vascular resistance in denoting serious pulmonary vascular disease had been shown by the tendency of such patients to have a high residual pulmonary artery pressure after closure. Cardiac catheterization studies six months to two years after operation showed pulmonary artery pressures very similar to those immediately after closure, suggesting that the fall in pressure after closure was due to reduction of pulmonary blood-flow and possibly to release of pulmonary arteriolar vasoconstriction. In patients with little or no fall in pressure it was assumed that severe pulmonary vascular disorder had been present, and it was not clear whether this would regress in subsequent years.

Clinical examination provided the best estimate of the degree of pulmonary vascular disease, the duration of the systolic murmur and thrill being the most sensitive guide. A low vascular resistance and slight vascular disease had been indicated by a long murmur and thrill, left ventricular type of cardiac impulse, and apical mid-diastolic flow murmur. A short ejection-type murmur and thrill, enlarged right ventricle, and loud pulmonary valve closure indicated severe vascular disease. Absence of a thrill and a very short murmur were signs of dangerously severe disease, and suggested that the fall in pressure after the closure of the defect was unlikely to be satisfactory. Patients with a resistance of over 8 units were in great need of operation, but the risks were high (about 20 per cent.), in contrast to 5 per cent. when the resistance was near to normal. However, 60 per cent. of the 'high resistance' patients survived. Operation had never been denied to a patient unless the physical signs were most unfavourable, the pulmonary: systemic flow ratio less than 1·5 to 1, or the shunt reversed.

Complete heart-block occurred in 15 patients, and was permanent in four. It tended to occur in patients with large defects and a high pulmonary vascular resistance, and was always transient when it occurred in patients with small defects and without pulmonary vascular disease. Death was attributable wholly or partly to complete heart-block in four patients. Associated lesions had been common, consisting of patent ductus arteriosus, mitral valve disease, aortic valve disease, or certain forms of transposition of the great vessels. Many of these lesions were difficult or impossible to diagnose clinically or by catheterization, and pre-operative selective angiocardiography was important, because the risks of operation could be greatly increased by associated lesions. In particular, a patent ductus arteriosus did not produce a clear murmur, a short early diastolic murmur being the only warning sign. The unexpected finding of a patent ductus in a hypertensive patient might be disastrous at operation, and aortography was necessary to make the diagnosis before operation.

DR. A. A. F. PEEL asked whether the development of complete heart-block was related to the site of the defect. Did the exact site of placement and tension of the sutures at the time of closure determine the subsequent development of block? In reply, DR. GOODWIN said that neither the site of the defect nor the number of sutures influenced the incidence of heart-block. Heart-block had sometimes occurred at the time of placing an individual suture, but reverted on removal of the suture. There was some evidence that the tighter the ligation, the greater the chance of heart-block, and the risk of this was less if the defect was less meticulously closed, although this increased the risk of a small residual shunt. The surgeon was therefore faced with the dilemma of deciding between tight suture of the defect with a greater risk of block, or a smaller risk of block and a greater risk of residual defect if the suture line was less tight.

9. *The Effect of Oestradiol on Hepatic Synthesis of Cholesterol in the Rat* was described by DR. R. PIERRE (introduced by DR. J. H. WRIGHT). To elucidate further the mechanism of oestrogen-induced hypocholesterolaemia, rats had been given 150 μg. of oestradiol benzoate per 100 g. body-weight per day for five days before the intraperitoneal injection of ^{14}C-labelled acetate, and sacrificed in groups of five at 2, 4, 12, 24, 48, and 60 hours later. Free and esterified cholesterol were isolated from plasma and liver by chromatography on silicic acid, and the weight and specific activity of each determined at the various time-intervals in both oestrogen treated and untreated controls. Oestradiol had produced a marked fall in both free and ester plasma cholesterol; this hypocholesterolaemia was accompanied by depression of cholesterol synthesis as measured by conversion of acetate to cholesterol, and by an increase in liver cholesterol, most of the increase being in the ester form. The radioactivity results had also indicated that the process of esterification of

cholesterol in the liver was more intense and more prolonged in the treated than in the control animals. In order to explain the association of hypocholesterolaemia with the increased ester-cholesterol in the liver of the oestrogen-treated animals, it was postulated that in addition to depressing cholesterol synthesis oestrogens altered the fatty-acid composition of liver cholesterol esters, perhaps by increasing the degree of saturation; these abnormal cholesterol esters might be less readily utilizable and transportable, and so accumulate in the liver cell, which continued to synthesize them, since there was a deficiency of utilizable esters. The findings emphasized that plasma cholesterol was not always a reliable index of tissue cholesterol.

In reply to DR. P. C. REYNELL, DR. PIERRE said that no observations had been made on cholesterol precursors.

10. DR. H. G. MILLER, and DR. D. POSKANZER and MR. A. E. BROWN (introduced) reported a case of *Musicogenic Epilepsy*. The patient was a 62-year-old civil servant subject to temporal-lobe fits, which occurred exclusively in response to the specific stimulus of church bells in the octave band centred at 800 cycles per second. The nature of his fits had come to light when he had a major convulsion just before the B.B.C. one o'clock news, and sustained a fracture-dislocation of the humerus. The case had been studied by a variety of modern acoustical techniques employing bell music, organ music, pure tones, and conventional and distorted piano music passed through a frequency-band selector which could be adjusted to cut out various frequencies. Of all the stimuli employed only church bells in this particular frequency were effective. After each musically induced convulsion there was a refractory period of about 12 days, during which the appropriate stimulus induced no disturbance. A successful stimulus produced a seizure within 30 seconds of its institution, and a paroxysmal electroencephalographic discharge from the left temporal lobe persisted from 90 to 100 seconds. Bell music appeared to have no particular significance in the patient's emotional life, and it would seem that these attacks were related to the acoustical character of the stimulus rather than to any associative quality—a situation encountered in some epileptic animals. A sound film was shown in which a synchronous electroencephalographic tracing was superimposed on the cinematograph picture of a seizure induced by playing a record of the B.B.C. interval signal. Treatment with epanutin has rendered the patient resistant to the epileptogenic effect of the stimulus.

DR. A. M. G. CAMPBELL said that rhythmic stimuli from other causes could produce this type of epilepsy, and he had an intelligent and non-neurotic patient who had epileptic attacks as she became conscious of the rather monotonous note of the great tit, particularly during the mating season. She also had attacks as a result of the ticking of a certain clock in her house. These two stimuli were quite specific, and nothing else produced attacks. As DR. MILLER had said, this type of stimulus appeared to resemble photogenically induced epilepsy, being induced by repeated monotonous auditory stimuli. Electroencephalographic studies showed a focus in the left temporal lobe. This type of epilepsy was different from that related to an emotional reaction following certain forms of music. DR. CAMPBELL had another patient who was unable to attend any concert performances of Brahms's or Beethoven's music without having an attack. A sedative taken before the concert would usually prevent an attack.

DR. R. HUGHES described a case of musicogenic epilepsy under his care. The patient was a choir-boy who had epileptic attacks during matins, the attack invariably occurring at the same point in the service. It had proved impossible to determine the precise sounds responsible. Perhaps these attacks were emotional rather than purely musicogenic in origin.

In reply to DR. H. DIMSDALE, DR. MILLER said that he had not investigated whether there was any difference in effectiveness between the two ears as peripheral receptors of the auditory stimuli.

11. DR. A. M. CONNELL (introduced), DR. F. AVERY JONES, and DR. E. N. ROWLANDS described some studies of *Abdominal Pain associated with Disturbed Intestinal Motility*, which had been greatly facilitated by the development of new techniques. Tube methods using either miniature balloons or open-ended tubes were satisfactory for investigating the motility of the sigmoid colon, but in less accessible areas of the gastrointestinal tract the 'radio pill' had many advantages. This device had been used as a diagnostic aid in patients with abdominal pain in whom no abnormality could be detected by routine investigation. A group of such patients was described who had periodic abdominal pain, usually after meals and associated with distension, flatulence, and more rarely nausea and vomiting. The discomfort might be sufficiently severe to require emergency admission to hospital, and three of the patients described had undergone emergency surgery with essentially negative findings. The motility response of the colon to eating in these patients was greatly

in excess of normal, and the hypermotility produced by food coincided with the occurrence of typical symptoms. It was suggested that the hypermotility was the result of an exaggerated gastro-colic reflex. Treatment with antispasmodics had been disappointing, but the spaced administration of sub-laxative doses of standardized senna had been of value.

In reply to DR. T. C. HUNT, DR. CONNELL said there was no obviously excessive secretion of mucus in the patients studied. DR. J. M. NAISH asked whether those suffering from severe post-prandial pain and colonic spasm were heavy smokers or drinkers, and whether smoking or alcohol caused a marked increase in intestinal motility. DR. CONNELL said that whereas no particular food could be incriminated, all the patients insisted that a good satisfying meal was more likely to produce symptoms than a less appetizing one. There was a suggestion that alcoholic drinks increased the likelihood of symptoms. In only one patient could smoking be considered a precipitating factor. In reply to DR. S. W. STANBURY he said he did not have any data on small intestinal motility in laxative addicts; and in answer to DR. R. D. TONKIN he reported that in the three patients studied there had been no increased secretion of 5-hydroxyindole acetic acid.

DR. R. W. LUXTON expressed the hope that these studies might throw some light on the pathogenesis of proctalgia fugax; but DR. CONNELL pointed out that it would be difficult to investigate such transient episodes of pain. DR. F. AVERY JONES commented that the motility pattern in patients with diarrhoea showed little or no activity, whereas those with constipation showed increased motility activity. 'Senokot' in a sublaxative dose, e.g. half a tablet three times a day, had the effect of reducing motility, and therefore might explain the benefit which had been noted in these patients.

12. *Ventilation Volume as Stimulus to Spontaneous Ventilation after Prolonged Artificial Ventilation* was discussed by DR. J. M. K. SPALDING (introduced by DR. W. RITCHIE RUSSELL). Observations had been made on paretic patients given artificial respiration by intermittent positive pressure through a tracheotomy. Tidal volumes of 500 to 1,000 ml. were used, and the end-tidal pCO_2 was kept constant by adding external dead space when the tidal volume was increased. The patients had subsequently been allowed to breathe spontaneously for periods not exceeding six hours in 24. During spontaneous respiration the external dead space had remained constant, approximately equivalent to the natural dead space eliminated by the tracheotomy. The patients' respiratory minute volume and end-tidal pCO_2 had been observed, and the ventilatory response to CO_2 added to the inspired air recorded. DR. SPALDING demonstrated that the respiratory minute volume during spontaneous respiration varied with the minute volume which had been imposed during preceding artificial respiration. He produced evidence that in these circumstances CO_2 was not the stimulus to respiration, and that it was ventilation volume itself which determined the level of spontaneous respiration. If the patient fell asleep and woke again, the volume-dependent type of respiration ceased, and a different level of respiration was adopted which was controlled by pCO_2. It was already known that respiratory volume was involved in the sensation of shortness of breath and in breath-holding, but this was the first time it had been shown to control spontaneous respiration.

DR. J. B. L. HOWELL said it was now recognized that conventional accounts of the organization of breathing were inadequate to explain some simple clinical observations. For example, after pneumonectomy the elastic work of breathing was considerably increased and yet the pCO_2 usually remained within normal limits without discomfort. This demonstrated that breathing was under non-chemical as well as chemical control. DR. SPALDING's observations showed not only that these two systems of control existed, but that they could be completely dissociated. This posed the question of the origin of the rhythmic breathing under these circumstances. He wondered if the conditions induced by DR. SPALDING resembled those existing in patients with the hyperventilation syndrome in which chemical control of breathing is replaced by other factors. Apart from the observations of the effect of sleep on this response, was there other evidence of disturbance of the reticular formation?

DR. H. A. DEWAR commented that the speed of spontaneous respiration following prolonged artificial respiration was not an organic phenomenon but the effect of autosuggestion derived from the previous experience of the artificial respiration rate.

DR. C. M. FLETCHER asked whether the ventilatory rate, as well as the volume, had been affected by the imposed respiratory rate of the artificial ventilation.

PROFESSOR STUART-HARRIS asked whether a similar phenomenon had been observed in patients with chronic chest disease treated with artificial ventilation.

DR. E. J. M. CAMPBELL asked whether DR. SPALDING had any suggestion to make about the site of the central mechanism responsible for this response. He said that hyperventilation disproportionate to chemical stimuli was seen clinically in patients with bilateral

or mid-line lesions in the upper pons. Did Dr. Spalding think the neural mechanisms lay here or elsewhere in the reticular formation?

In reply, DR. SPALDING said that presumably the mechanism of the volume-dependent type of respiration involved changes in the alerting system of the brain produced by the previous ventilation with large volumes. The reticular formation was probably involved. The respiratory frequency during spontaneous respiration was usually one or two breaths more per minute than during artificial respiration. He had not had the opportunity to repeat the observations on patients with chronic chest disease. He did not think that the volume-dependent type of respiration was psychologically determined. There was no motive to induce the patients to breathe in this way, and as they could not see the anemometer it was almost impossible for them to breathe in this way with anything approaching the accuracy observed. He was not prepared to say whether tidal volume or minute volume was the important factor.

13. An account of the *Inheritance of Idiopathic Haemochromatosis* was given by DRS. R. WILLIAMS and P. J. SCHEUER (introduced by PROFESSOR SHEILA SHERLOCK). All the available siblings and children of 14 patients with haemochromatosis had been examined; investigations included estimation of the serum iron level, liver-function tests, and liver biopsy. The last procedure proved the most sensitive in diagnosis, a positive reaction for free iron being obtained in 26 of the 40 relatives examined. In three others the presence of excess of iron was demonstrable only by electron microscopy. Taking a positive liver biopsy as the criterion of involvement, multiple siblings or children were affected in 11 of the 14 families. The condition appeared to be transmitted as a Mendelian dominant, and in one family could be traced through four generations. In the three families in whom no hereditary defect could be demonstrated, siblings were not available for testing and the children examined were in the younger age groups. The serum iron level had been less reliable in diagnosis. Although the mean level in affected relatives was higher than in unaffected members, there was a considerable overlap. Liver-function tests had been normal except for bromsulphalein retention, which was increased in 30 per cent. of the affected relatives. The clinical picture of the affected siblings and children was very variable. Pigmentation of the skin, either generalized or around recent scars, was often the only physical sign. One had diabetes. Definite cirrhosis was found in only one case, although in six others there was portal-tract infiltration and fibrosis. Other abnormal histological features were a high incidence of fatty change and the presence of increased amounts of lipofuscin or 'wear and tear' pigment. It was stressed that this variation in the clinical picture was partly the effect of age, and in general the older the patient the more marked the changes. Nevertheless, environmental factors were probably of importance, and in particular alcoholism, six of the 14 propositi being heavy drinkers as opposed to two of the affected relatives. It was concluded that the detection of these early cases was of considerable importance, as treatment by venesection might prevent further progression of the disease.

PROFESSOR SIR ROBERT PLATT asked whether the gene concerned in haemochromatosis might be intermediate in its expression, with three phenotypes; the normal homozygote, the affected homozygote, and the heterozygote showing the minor manifestations only detected by liver biopsy and other investigations. In the case of a rare gene the siblings of a case of haemochromatosis should then show a 1:2:1 ratio. The figures given seemed compatible with this theory, except in the case of the Canadian woman with haemochromatosis who had one normal child. In reply, DR. WILLIAMS said that before much reliance could be placed on these figures all the members of each generation would have to be examined, and this had not been possible. The effect of age had also to be taken into account in assessing the numbers affected. In answer to DR. R. W. PARNELL, who wondered whether there had been difficulty in persuading apparently healthy persons to undergo a liver biopsy, DR. WILLIAMS emphasized the importance of establishing a diagnosis if treatment was to be started at an early stage. DR. SHEILA CALLENDER asked whether iron absorption for the detection of early cases had been studied, but DR. WILLIAMS was only just collecting this information. In reply to DR. C. M. FLETCHER he said the effect of venesection was being compared with an untreated control group. DR. J. C. HOUSTON commented that in his experience the degree of saturation of the serum iron-binding capacity was more helpful in the diagnosis of haemochromatosis than the serum iron level, and asked whether the liver biopsy findings had been correlated with this. In reply, DR. WILLIAMS said studies of the iron-binding capacity had been made in only some families in the series, and those patients with normal serum iron levels had also had normal binding capacities.

14. DR. E. J. M. CAMPBELL and DR. J. B. L. HOWELL (introduced by PROFESSOR A. KEKWICK) discussed *Rebreathing Methods for the Measurement of Blood* pCO_2. The blood

pCO_2 was shown to be dependent on the balance between body CO_2 production and CO_2 excretion through the lungs. Thus the blood pCO_2 was the only indisputable index of the adequacy of pulmonary ventilation. Arterial pCO_2 had in the past appeared to be the measurement of choice, but was technically difficult. Collier had realized that the difference in pCO_2 between the arterial and mixed venous blood was small in resting subjects, and had introduced a rebreathing method using a rapid analyser in which pCO_2 was equilibrated between a small bag, the lungs, and the pulmonary arterial (mixed venous) blood. This principle could be applied without requiring a rapid CO_2 analyser if a two-stage procedure were used. In the first stage the subject 'prepared' a CO_2 mixture by rebreathing 100 per cent. O_2 for about one and a half minutes; in the second stage this was equilibrated with the mixed venous blood by rebreathing from the same bag for about 20 sec. The volume of the bag that should be used, and the manner in which the procedure should be varied to suit patients with different depths of breathing, were emphasized. The aim should always be to have the volume of gas in the bag less than twice the tidal volume of breathing. It was sufficient to judge this by eye.

Dr. C. M. Fletcher asked what precautions were taken to avoid leaks around the mouthpiece. He had found this to be difficult in some seriously ill patients, and there was danger of getting falsely low values. Dr. Campbell showed how leakage could be avoided by using a large flange on the mouthpiece.

Dr. K. N. V. Palmer inquired whether this technique was satisfactory in patients with obstructive emphysema, because in this condition the distribution and mixing of inspired gases was usually uneven. Dr. Campbell agreed that some aspects of the disturbed pulmonary function in emphysema hindered the equilibration procedure, but pointed out that other aspects facilitate it, and experience had shown no significant difficulty in applying the method in patients with emphysema. In answer to Professor J. Crofton he said the best way of checking the accuracy of a measurement was to repeat the procedure using smaller volumes and longer times.

Professor Stuart-Harris said the rebreathing method had been used in Sheffield, and preliminary difficulties overcome once a CO_2 analyser was available. The procedure was extremely valuable. Dr. J. Macrae said he had been using the technique for two years, and had found it quick and accurate. He had compared results with those obtained by estimation of arterial pCO_2, and there had been close agreement. In reply to Professor A. V. Neale, Dr. Campbell said the smallest patient on whom he had used the method was a girl aged three with a tracheostomy, but he believed it had been used in infants with tetanus neonatorum. He stressed that the volume of bag used must be greatly reduced.

Before lunch sherry was kindly provided by the University. In the afternoon members and their wives visited Bath, the Wildfowl Trust at Slimbridge, and Berkeley Castle.

NOTICE

The Index to Volumes XXI to XXX will be issued in January 1962

CORRECTION

Volume 30, page 210 (No. 118, April 1961)

In the paper on *The Genetics of Pseudoxanthoma Elasticum* by G. M. Berlyne, M. G. Bulmer, and R. Platt, the following correction should be made. The second sentence under the heading *Family He* should read 'he has previously been reported by Edwards (1958) who excised a small piece of the stomach because of gastrointestinal bleeding.'